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Diagnosis and treatment of primary CNS lymphoma in immunocompetent patients: guidelines from the European Association for Neuro-Oncology

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Dear Editor,

Thank you for your suggestions to improve further our paper. Please, find in attached file our revised manuscript which have take into account all your editorial recommendations. You will find below our point by point replies to your editorial comments. We hope that you will find now the manuscript suitable for publication in Lancet Oncology.

Kind regards

Khe Hoang-Xuan, MD,PhD

Responses to the Editor comments

1) In response to Reviewer 1, comment 2, please revert and move the intraocular lymphoma section back to the appendix as in the original version.

RESPONSE: The intraocular lymphoma section is now back to the appendix with the corresponding references

2) In response to your reply to Reviewer 2, comment 1, please leave the tables as they are.

RESPONSE: OK

3) In response to your reply to comment 3 from Reviewer 3 (regarding guidelines for treatment of patients for which there are no evidence based recommendations), please summarize your reply and add it to the text to clarify that it is not possible to provide evidence-based recommendations for patients with tumours that cannot be or are too risky to biopsy.

RESPONSE: Two sentences have been added in the general recommendation section (p.4)

"Our guideline covers treatment of histologically or cytologically proven PCNSL. We have not covered specifically the treatment of patients with deep seated tumours not readily amenable to biopsy for which there are no evidence-based recommendations. We believe that biopsies are almost always possible in specialized centers and that chemotherapy and/or radiotherapy interventions without histological confirmation of PCNSL should be discouraged."

EANO Guideline for the diagnosis and treatment of primary CNS lymphoma in immunocompetent patients.

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Abstract

The management of primary central nervous system (PCNSL) is one of the most controversial topics in neuro-oncology because of the complexity of the disease and the very limited number of controlled studies available. In 2013, the European Association of Neuro-Oncology (EANO) created a multidisciplinary task force to establish evidence-based guidelines for immunocompetent adult patients with PCNSL. The guideline provides consensus considerations and recommendations for diagnosis, staging and treatment of PCNSL, including surgery, systemic and intrathecal chemotherapy, intensive chemotherapy with autologous stem cell transplantation, radiotherapy, intraocular manifestations, and specific management of elderly patients. The guideline should aid the clinicians in everyday practice and decision making and serve as a basis for future research in the field.

Introduction

Primary central nervous system lymphomas (PCNSL) are extranodal malignant non-Hodgkin lymphomas (NHL) of the diffuse large B cell (DLBCL) type confined to the brain, eyes, leptomeninges, or spinal cord in the absence of systemic lymphoma. Currently PCNSL are estimated to account for up to 1% of lymphomas, 4-6% of all extranodal lymphomas, and about 3% of all CNS tumors.¹ After a continuous increase in the 1980's and 1990's, epidemiologic data in Western countries show a decrease in the incidence of PCNSL, particularly among young patients suffering from AIDS.² In contrast, the incidence continues intriguingly to rise in the elderly who represent consequently the large majority of patients in the immunocompetent population in some recent studies.³⁻⁵ Although the prognosis of PCNSL remains poor, it has significantly improved over the past two decades as a result of better treatment strategies with a curative aim. Treatment of PCNSL is challenging. Despite a high chemosensitivity and radiosensitivity, remissions are frequently short-lasting; the blood brain-barrier (BBB) limits the access of many drugs to the CNS; and patients, especially the elderly, are at high risk of developing severe treatment related-neurotoxicity. To date, therapeutic knowledge to define the optimal treatment mainly results from retrospective series or single arm phase II studies, with only three completed randomized trials available: one phase III and two phase II. The objective of this guideline is to provide clinicians with evidence-based recommendations and consensus expert opinions on the management of patients with PCNSL. The present guideline focuses on the immunocompetent population which represents the vast majority of the patients today. PCNSL of immunodeficient patients and the rare indolent low grade lymphomas occurring primarily in the CNS, which have a distinct pathogenesis with separate diagnostic and therapeutic implications, will be subject to specific guidelines.

Search strategy and selection criteria

The guideline task force was set up in 2013 under the auspices of the EANO (European Association for Neuro-Oncology) and selected to be representative of European-based medical experts (10 countries). The panel covered all fields of expertise in the management of PCNSL, i.e. neurologists, haematologists, medical oncologists, neurosurgeons, pathologists, ophthalmologists and radiation oncologists. Based on best available evidence from literature review, the writing group (EB, JB, AH, KHX, MP, RR, US, TS, CS) produced the draft guideline, which was subsequently submitted to the review committee (UA, NC, MD, CD, AF, FG, RH, UH, RS, MT, MW). The revised guideline, taking into account the comments of the reviewers, was resubmitted by the chairman to the whole task force for review and amendments twice. Thereafter, final agreement was obtained in September 2014. When

analyzing results and drawing recommendations, at any stage, differences were resolved by discussion and, if persisting, were reported in the text. References for this review were identified through searches of PubMed with the search terms "primary CNS lymphoma", "primary central nervous system lymphoma", "primary intraocular lymphoma", "elderly", "radiotherapy", "chemotherapy" and "rituximab" from January 1980 to September 2014. Articles were also identified through searches of the authors' own files. The final reference list was generated on the basis of originality and relevance to the broad scope of this review. Abstracts presented at the annual ASCO meeting in 2013 and 2014 relevant to the topic were included by task force members during manuscript preparation. The scientific evidence of papers collected from the literature was evaluated and graded as follows and recommendations were given accordingly. Class I evidence was derived from prospective, randomized, phase III clinical trials; class IIa evidence was derived from prospective randomized phase II trials, class IIb evidence was derived from phase II trials; class IIIa was derived from prospective studies, including observational studies, cohort studies and case-control studies; class IIIb evidence was derived from retrospective studies; class IV evidence was derived from uncontrolled case series, case reports and expert opinion. As for recommendations, level A required at least one class I study or two consistent class IIa studies, level B at least one class IIa study or overwhelming class IIb and III evidence and level C at least two consistent class III studies. Pathology, genetics, clinical features and neuroimaging were simply reviewed but not graded. When sufficient evidence for recommendations A–C was not available, we gave a recommendation as a "Good Practice Point", if agreed by all members of the Task Force.

General recommendations

Consensus statements and recommendations for the general approach to patients with PCNSL, including: 1/ pathology and genetics, 2/ clinical presentation, 3/ diagnostic confirmation, 4/ neuropathology of corticosteroid-treated PCNSL, 5/ neuroimaging, 6/ cerebrospinal fluid (CSF) analyses, 7/ vitreous analyses, 8/ staging, 9/ prognostic factors, 10/ response criteria to treatment, and 11/ treatment-related neurotoxicity are presented in table 1. The evidences used to establish these recommendations are detailed in the supplementary webappendix. Key recommendations for treatment are summarized in table 2. The evidences concerning intraocular lymphoma are presented in the webappendix. Our guideline covers treatment of histologically or cytologically proven PCNSL. We have not covered specifically the treatment of patients with deep seated tumours not readily amenable to biopsy for which there are no evidence-based recommendations. We believe that biopsies are almost always possible in specialized centers and that chemotherapy and/or radiotherapy interventions without histological confirmation of PCNSL should be discouraged.

Surgery

Although very few data are available in the literature, surgery has traditionally been considered to have no role in the treatment of PCNSL. This widely adopted opinion is based on small retrospective series suggesting no clear benefit in outcome of surgical resection used as sole treatment compared with supportive care (Class IIb),⁶ and compared with biopsy in patients having received post-operative chemotherapy and/or radiotherapy (Class IIb).^{7,8} This may be explained by the microscopically multifocal and infiltrative nature of PCNSL that may extend beyond the visible border of the lesion.⁹ The relative radiosensitivity and high chemosensitivity of PCNSL, and the increased risks of postoperative morbidity of this patient population have also contributed to discourage surgery. However, the recommendation to restrict surgical interventions to biopsies is not based on randomized data and, more importantly, not on contemporary data reflecting modern neurosurgery. The German PCNSL Study Group–1 phase III trial included an unusually high rate of operated patients, which allowed the largest and most recent retrospective analysis of an association of surgery and outcome. A significantly longer progression free survival (PFS) and overall survival (OS) in patients with subtotal or gross total resections compared with biopsied patients was reported. This difference in outcome was independent of post-operative Karnofsky performance status (KPS) and age. Since biopsied patients more often had multiple and/or deeply seated CNS lesions than resected patients, these features may have contributed to the unfavourable outcome. When adjusted for the number of lesions (site of the lesions was not analyzed in the study), the difference in outcome remained significant in term of PFS but did not reach the significance threshold for OS (Class IIIa).¹⁰

Systemic chemotherapy

The CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) regimen commonly used for systemic NHL induces short-lasting responses in PCNSL and its addition to radiotherapy has not shown a survival benefit in prospective trials (Class IIb).¹¹⁻¹³ This inefficacy is probably due to the fact that phosphoramidate mustard and doxorubicin are not able to cross the blood-brain barrier (BBB) to eradicate microscopic disease. Based on convergent results from numerous prospective and retrospective studies, high-dose (HD) intravenous (iv) methotrexate (MTX), an antifolate and antimetabolite, is now considered the most important and beneficial single agent. Penetration of MTX into the CNS depends both on the total dose and rate of infusion. The optimal dose of MTX has not been determined. It has been estimated that the iv MTX should range between 1 g/m² and 8 g/m² to cross the BBB. In the absence of clear evidence for dose-response relationship, and since rapid infusion of MTX $\geq 3\text{g/m}^2$ over 3 hours achieves cytotoxic levels in the CSF, there is a growing consensus to deliver MTX according to this protocol (Class IV).¹⁴ Since efficacy of MTX may also depend on duration of exposure, MTX administration interval should range between 10 days and 3

weeks (Class IV).¹⁵ The optimal number of MTX injections to deliver is unknown. A minimum of 4-6 injections is delivered in most chemotherapy regimens, especially if no consolidation treatment (radiotherapy and/or intensive chemotherapy) is scheduled in the protocol. For patients who achieved only partial response (PR) after 4-5 courses of HD MTX, additional courses may improve the complete remission rate (Class IIIa).¹⁶ Infusions of HD MTX require pre- and post-hyperhydration, urine alkalinization, leucovorin rescue and MTX concentration monitoring. Currently most treatment protocols combine HD MTX with a variety of other chemotherapeutic agents to improve response rate and outcome. The best evidence to support this approach comes from an IELSG randomized phase II study comparing HD MTX alone, administered at 3 g/m²/d every 21 days, to HD MTX with cytarabine (2 g/m² twice per day on days 2–3)(Class IIa).¹⁷ Both chemotherapy arms were followed by WBRT. This study showed a significantly higher complete response (CR) rate in the HD MTX-cytarabine arm. Regarding secondary endpoints, a significantly improved overall response rate (ORR), PFS and a trend towards better OS in the HD MTX-cytarabine arm were noticed. Two previous prospective trials evaluating HD MTX at a dose of 8g/m² as single agent and without immediate consolidation WBRT resulted in a shorter PFS when compared to polychemotherapy regimens (Class IIb).^{18,19} Similarly, the addition of ifosfamide to HD-MTX improved response rate, but not survival, in the G-PCNSL-SG-1 trial.²⁰ Altogether, these data resulted in the recognition that only HD MTX can be defined as a chemotherapy standard of care.²¹ Chemotherapeutic agents to be combined with HD MTX should be selected among active drugs known to cross the BBB, such as HD cytarabine. Recently, the CALGB50202 multicenter phase II trial reported promising results using HD cytarabine combined with etoposide as consolidation without WBRT following a HD MTX-based polychemotherapy as induction regimen (Class IIb).²² In contrast, very disappointing results have been reported in a pilot study combining HD MTX (3.5g/m²), thiotepea and cytarabine at a reduced dose of 1g/m² suggesting that the cytarabine dose probably was suboptimal to reach cytotoxic levels in the CNS (Class IIIa),²³ as supported by pharmacokinetic studies.²⁴ Another approach is BBB disruption (BBBD) by intra-arterial (IA) infusion of hypertonic mannitol followed by intra-arterial (IA) chemotherapy to increase the drug concentration in the CNS. BBBD with IA MTX administrated in newly diagnosed PCNSL demonstrated a good safety profile and neurocognitive tolerance and achieved comparable outcomes to those observed with HD-intravenous MTX based chemotherapy regimens (Class IIIb).²⁵⁻²⁷ However, conversely to those reported in prospective studies on chemoradiotherapy, even after a follow-up longer than 10 years (Class IIb),²⁸ BBBD is not associated with a plateau in survival curves, suggesting a continuum of relapses and deaths. This procedure requires patient selection as safety depends on the extent of intracranial mass effect and the procedure is limited to patients with no contraindications for general anesthesia. It should be managed by teams trained in BBBD as it is complex, requiring cannulation of the intracranial vessels. In summary, HD MTX is the drug of choice for PCNSL. In patients who are not eligible for HD MTX, treatment should be chosen from treatments

active as salvage in refractory or recurrent PCNSL after initial HD MTX based chemotherapy (see salvage treatment section).

Intrathecal chemotherapy

Intrathecal (IT) chemotherapy administration has not been prospectively studied and its efficacy in PCNSL remains debated. Three retrospective studies did not demonstrate benefit from the addition of intrathecal drugs (MTX, cytarabine) in patients treated with HD MTX dosed at 3g/m^2 (Class IIIb).²⁹⁻³¹ In contrast, two consecutive single arm trials using the same systemic polychemotherapy regimen suggested additional benefit when intraventricular chemotherapy was added (Class IIIa).^{32,33} However, given the low level of evidence, we currently do not advocate IT chemotherapy as prophylaxis.

Rituximab

Based on its poor penetration into the CNS related to its large size, the maximal concentration and efficacy of the anti-CD20 antibody rituximab in the CNS might be assumed to occur in the early treatment phase, during BBB breakdown within the tumors. The effect of rituximab when used as monotherapy in PCNSL was evaluated in a single study in which 12 patients with refractory or relapsed PCNSL were treated with a weekly iv dose of 375 mg/m^2 rituximab infusion for up to eight doses (Class IV).³⁴ MRI responses were observed in 36% of patients. Other studies used iv rituximab in combination with a HD MTX-based chemotherapy regimen as initial treatment for newly-diagnosed PCNSL or as salvage treatment for recurrent PCNSL (Class IIIa, Class IIIb and IV).^{16,22,35-41} Three studies suggested that the addition of rituximab to HD MTX-based chemotherapy improves the CR and OS rate in patients with newly-diagnosed PCNSL based on retrospective comparison with historical controls (Class IIIb).³⁹⁻⁴¹ Overall, the addition of rituximab to systemic polychemotherapy is well tolerated. Injection of rituximab into the CSF via either lumbar puncture or by intraventricular administration was evaluated in phase I for refractory or recurrent CNS lymphoma patients (Class IIIa).⁴² In these studies objective responses and good tolerability were documented confirming small case series. In conclusion, the existing level of evidence supporting either systemic or local use of rituximab as part of treatment protocol for PCNSL remains low. Yet, the preliminarily available information suggests that it may add some benefit. Two ongoing randomized trials (NCT01011920; NTR2427) should clarify the role of systemic rituximab in PCNSL.

Radiotherapy

Because of the microscopically diffuse and multifocal nature of PCNSL, radiotherapy (RT) has so far involved the whole brain, including the eyes. Despite a high response rate in the range of 50%, RT used as sole treatment modality, provides limited survival benefit in PCNSL patients, with a median OS duration of 10–18 months and a 5-year survival rate of 5%. The only phase II trial, conducted by the RTOG, which delivered a total dose of 40 Gy with an additional 20-Gy boost to contrast-enhancing lesions, reported a disappointing 11.6 month OS (Class IIb).⁴³ In addition, the majority of relapses occurred in fields that had received the highest RT dose. Although not formally compared in a randomized trial, a wide consensus is shared which considers that HD MTX-chemoradiation is superior to RT-alone, allowing for a 2 to 4-fold increase in OS (median: 30-72 months) and long-term survivors (5-year survival of 20-50%) for many protocols (Class IIb, IIIa IIIb).^{15,44-52} In contrast to extracerebral NHL, the optimal dose of post-chemotherapy irradiation has never been prospectively investigated in PCNSL.⁵³ Doses of 23–50 Gy to the whole brain, with or without a tumor bed boost, are currently used, with most of the protocols delivering a total dose of 40–45 Gy without boost, and standard fractionation (1.8-2Gy/fraction). The RTOG-9310 trial did not show a clear benefit with hyperfractionated WBRT (Class IIb).⁵⁴ For patients who achieve a CR after HD MTX-based chemotherapy, it remains unclear whether consolidation with WBRT provides better disease control or survival. There has only been one randomized trial of radiotherapy versus watch-and-wait after chemotherapy for PCNSL. This study (G-PCNSL-SG 1) conducted in Germany was a non-inferiority phase III trial, in which patients received HD MTX 4g/m² iv every 14 days for 6 cycles with or without ifosfamide. Those patients who achieved a CR had been randomized initially between consolidating WBRT, 45 Gy in 30 fractions over 6 weeks or no further immediate treatment. Patients without a CR received HD cytarabine or WBRT. A total of 551 patients entered the study, but 318 patients were treated per-protocol. OS was similar in both arms. In the whole per-protocol population, the WBRT arm was associated with a trend (not significant) for better PFS, as compared with the no WBRT arm but with no significant difference in OS.²⁰ This trial (Class I), which is, to date, the largest one and only phase III trial in PCNSL has raised vigorous debate within the community.⁵⁵⁻⁵⁸ Several experts consider that the unmet primary endpoint for non-inferiority and the high rate of protocol violations prevent any conclusions being drawn from the trial and advocate keeping consolidation WBRT after HD MTX-based chemotherapy as the standard of care, whilst awaiting results from further, ongoing randomized trials; while others, acknowledging the methodological limitations of the study, consider nevertheless that the results contribute strongly to the accumulating retrospective literature suggesting that omission of WBRT from first-line treatment results in shorter PFS but does not compromise OS (Class IIIb).^{29,59,60} In addition, several single arm trials have suggested that chemotherapy alone, plus a deferred RT strategy may result in comparable OS with those reported for combined chemo-RT but with better neurocognitive preservation (Class IIb, IIIa, IIIb).^{19,25,26,32,61-63} Since withdrawing consolidation WBRT for patients with CR to chemotherapy remains controversial, especially in patients less than 60 years old who are at lower risk of developing neurotoxicity, reduced

dose WBRT is another alternative approach. Conflicting results have been reported. A subset analysis from a phase II trial that included 25 patients aged <60 years who achieved a CR after initial chemotherapy and received either 45 Gy or 30.6 Gy as consolidation treatment showed a significantly higher recurrence rate and lower OS rate in the reduced-dose RT group (Class IIIb).⁶⁴ On the other hand, in a retrospective study of 33 patients with PCNSL who achieved CR after MTX-containing chemotherapy and were referred to consolidation WBRT, total doses ≥ 40 Gy were not associated with improved disease control in comparison with a WBRT dose of 30-36 Gy (Class IIIb).⁶⁵ More recently, a phase II trial evaluating an immunochemoradiation regimen (R-MPVA) including rituximab and HD MTX-based polychemotherapy, the 31 CR patients were offered reduced dose WBRT (23 Gy in complete responders) with encouraging results both in term of survival and neurotoxicity (Class IIb).¹⁶ Based on these results, a randomized phase II study (RTOG-1114) comparing the R-MPV regimen with or without reduced-dose WBRT is currently ongoing (NCT01399372). In summary, the role of consolidation WBRT following HD-MTX based chemotherapy remains debated especially in patients in CR. In addition, the optimal dose has not been defined yet.

High-dose chemotherapy, myeloablative conditioning and autologous stem cell transplantation (HDC/ASCT)

HDC/ASCT is the standard treatment for chemosensitive relapsing systemic DLBCL. For patients with relapsed or refractory PCNSL, there is only one multicenter phase II trial evaluating HDC/ASCT, with TBC conditioning regimen (thiotepa, busulfan, cyclophosphamide). The CR rate was 60%, median PFS and OS were 41 and 58 months respectively for the 27 patients out of 43 who completed the full HDC/ASCT procedure. For the whole population of this trial, the intent-to-treat median PFS and OS times were 11 and 18 months respectively. The toxicity-related mortality was 7% (Class IIb).⁶⁶ An update of this study to which additional cases have been included, and an independent retrospective single center series confirmed the benefit of the TBC regimen followed by ASCT (Class IIIb).^{67,68} Experiences with other HDC regimens in this setting of patients are limited to a few cases, which prevent any conclusions being drawn. Because of its toxicity risks, the HDC/ASCT is likely to be proposed for younger patients (<60-65 years) with a good performance status, which makes it difficult to compare with other salvage treatments, including second-line conventional chemotherapy regimens and WBRT. The specific role of HDC/ASCT as consolidation in first-line treatment is difficult to evaluate since WBRT was administered after HDC/ASCT in early studies (Class IIb).^{69,70} The first study with HDC/ASCT without WBRT used the BEAM regimen (BCNU, etoposide, cytarabine, and melphalan) as conditioning and reported a disappointing median event-free survival of 9.3 months (Class IIIa).⁷¹ Subsequently, encouraging studies for which WBRT had been omitted at least in patients in CR after HDC/ASCT using HD thiotepa-based conditioning regimens have been reported (Class IIIb and IV).⁷²⁻⁷⁵ Taken together, although direct comparison between conditioning

regimens applied is difficult, HD thiotepa-based conditioning regimens seem more efficient than BEAM-based regimens. In summary, HDC/ASCT represents an effective treatment option for selected refractory and relapsed PCNSL patients, but should be reserved to experienced centers. Superiority of the HDC/ASCT approach compared to standard combined chemo-radiotherapy as first line treatment has not been proven and is currently under investigation in two ongoing trials (NCT00863460, NCT01011920).

Elderly patients

Definition of 'elderly' is not uniform. However, in the studies available which have evaluated prognostic factors, older ages (over 50 and over 60) were consistently correlated with worse outcome (see the section on prognostic factors in appendix). Furthermore, for chemoradiation-induced neurotoxicity age>60 was found to be highly prognostic (see the section on neurotoxicity in appendix). Therefore, age of 60 has been used as cut-off to define the elderly population in most of the studies. Four prospective studies have been published on treatment of elderly patients with PCNSL (Class IIb),^{36,63,76,77} seven prospective studies on patients of all ages but reporting specifically on older patients (Class IIIa),^{11,12,32,43,52,54,78} and seven retrospective studies reporting on ≥ 15 patients (Class IIIb).⁷⁹⁻⁸⁵ As in younger patients, results in patients treated with steroids or CHOP/CHOD in addition to radiotherapy do not differ from results after radiotherapy only (Class IIb).^{11,12,43,77} In the RTOG phase II trial, the median survival was only 7.8 months.⁴³ After HD-MTX-based therapy, defined as dose of MTX $\geq 1 \text{ g/m}^2$ PFS in patients aged 60 or 65 and older is reported between 6 and 16 months and OS between 14 and 37 months (Class IIb and Class III) with OS in the majority of prospective studies under 2 years.^{32,36,52,54,63,73,78-85} Other than within retrospective studies no direct comparisons have been made between treatment with HD-MTX-based chemotherapy and radiotherapy in this age group.⁸¹ However, the impression from the single arm studies is that survival after chemotherapy is at least as good and probably better after HD MTX-based chemotherapy than after radiotherapy (Class IV). Formal comparisons of different HD MTX-based regimens have not been published but in a recently completed randomized phase II study, toxicity was identical, CR rate, median PFS and survival appeared better after MPV-A (MTX, procarbazine, vincristine, cytarabine) than after MTX and temozolomide though the difference was not significant (Class IIa).⁸⁶ Five prospective studies report on chemotherapy toxicity in patients aged over 60. With the exception of one study, in which an intensive multi-drug regimen was used and toxicity was exceedingly high in older patients,⁵² HD MTX-based chemotherapy up to 3.5 g/m^2 was well tolerated with 2-7% treatment-related mortality, less than 10% grade 3-4 nephrotoxicity and 7-10% of patients discontinuing treatment due to chemotherapy-associated toxicity, though MTX dose was reduced because of decreased renal function in 26-44% of patients.^{36,63,76,87} Retrospective studies substantiate this view. Thus, in general, older patients tolerate treatment with HD-MTX well when adequate supportive measures are used and renal

function is accurately monitored.³ As discussed in the neurotoxicity section (appendix), risk of delayed leukoencephalopathy is particularly high in patients older than 60 years managed with chemoradiotherapy. For patients treated with HD-MTX-based chemotherapy without radiotherapy no studies reporting specifically on older patients are available, but reports including neuropsychological assessment of patients of all ages show little or no cognitive decline compared with post-treatment evaluations (Class IIb).^{61,88} Given the available data on acute and long-term toxicity of radiotherapy and chemotherapy in older patients with performance status KPS \geq 70, treatment with HD MTX-based chemotherapy with deferral or elimination of WBRT is the treatment of choice. In older patients in poor condition and in the very old (over 80) who both have a worse prognosis,⁸⁵ the acute morbidities and frequent admissions to hospital associated with HD-MTX chemotherapy need to be individually weighed against the more limited survival benefits in this population.

Salvage treatment

About one third of patients with PCNSL will present with disease that is refractory to first-line treatment and half of responders will relapse despite high response rates seen with initial treatment. The prognosis of progressive or relapsed PCNSL remains poor with limited treatment options. Salvage treatments for relapsed or refractory PCNSL patients depend on age, performance status, site of relapse within the CNS, prior treatments and time duration from last response. If the patient did not receive any consolidating treatment after the HD MTX-based induction chemotherapy, WBRT or HDC/ASCT should be considered. Two retrospective studies have evaluated WBRT delivered in relapsed PCNSL and reported a high rate of objective responses and a short median survival of 11-16 months - quite similar to what is expected with WBRT alone as initial treatment (Class IIIb).^{89,90} Delayed neurotoxicity occurred in 15%–22% of patients. However, in the setting of recurrence, WBRT did not prolong survival compared with non-WBRT-based therapies in the G-PCNSL-SG-1 trial (Class IIIa).²⁰ HDC/ASCT is an efficient alternative option, as has been previously discussed, and which should be preferentially proposed for patients aged < 60-65 years and with a tumour sensitive to second-line chemotherapy (Class IIb) (see section above).⁶⁶⁻⁶⁸ Otherwise, if the patient is not suitable for WBRT or HDC/ASCT, conventional chemotherapy can be proposed as second-line treatment. There is however, only a limited number of prospective studies available for guidance and these have been single-arm phase II trials complicating any comparison across trials (Class IIb, III and IV for all studies in this section). Several drugs used as single agent or in combination, with or without rituximab, have been evaluated and demonstrated modest activity such as temozolomide,^{38,91} topotecan,⁹² pemetrexed,⁹³ bendamustine,⁹⁴ PCV regimen,⁹⁵ ifosfamide-etoposide based regimen,^{37,96} or cisplatin-cytarabine based regimen.⁹⁷ MTX rechallenge given as single agent or in combination may also yield a high rate of new objective response and durable remission in patients who previously achieved prolonged response with HD MTX-based chemotherapy, suggesting retained

chemosensitivity to MTX (Class III).^{98,99} Extra-CNS relapses account for 7% of failures, and some studies suggest that extra-CNS relapses are associated with a better prognosis than CNS-involving relapses;¹⁰⁰ the best salvage treatment for this condition remains to be defined, but excellent results have been reported with anthracycline-based chemotherapy consolidated or not with HDC/ASCT.²⁸

Conclusions

Guidelines reflect the state of knowledge at a given timepoint. The EANO website will inform of future updates on this guideline (<https://www.eano.eu>).

Contributors

KHX chaired the task force. Based on best available evidence from literature review, the writing group (EB, JB, AH, KHX, MP, RR, US, TS, CS) produced the draft guideline, which was subsequently submitted to the review committee (UA, NC, MD, CD, AF, FG, RH, UH, RS, MT, MW). The revised guideline, taking into account the comments of the reviewers, was resubmitted by the chairman to the whole task force for review and amendments twice.

Declaration of interest

KHX was the principal investigator of a trial investigating temozolomide (Scherring-Plough) in PCNSL and declare no competing interest. UA reports personal fees from Varian and BrainLAB AG outside the submitted work. MP reports grants from GSK, Roche, Böhringer-Ingelheim, personal fees from GSK, Roche, BMS, outside the submitted work. US reports personal fees from Roche, Medac, GSK, outside the submitted work. MT reports honoraria ad hoc consultancy for Hoffmann La Roche, outside the submitted work. MW reports grants and personal fees from Roche, Merck Serono, Isarna, Novocure, grants from Bayer, Piquir, personal fees from Celldex, Magforce, outside the submitted work. EB, JB, FG, AH, NC, RR, AJMF, MD, CD, TS, RS, CS, declare no competing interest.

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Table 1: Consensus statements and recommendations for the general approach to patients with PCNSL including establishment of diagnosis, baseline work-up and response to treatment

Diagnosis

- Cranial MRI with FLAIR and T1 weighted sequences before and after contrast injection is the neuroimaging method of choice for the diagnosis and follow-up of PCNSL. Diffusion, dynamic susceptibility contrast, proton spectroscopy MRI, and FDG-PET can be useful in the differential diagnosis but are not specific (Good Practice Point).
- The diagnosis of PCNSL requires pathological confirmation before treatment (Good Practice Point).
- When PCNSL is suspected, the standard surgical procedure for diagnosis is a stereotactic or navigation guided needle biopsy (Good Practice Point, see section on surgery for discussion).
- Because it may prevent the histopathological diagnosis, it is recommended, if clinically possible, to avoid steroids before biopsy. In case of remission and/or unspecific inflammation in the tissue biopsied in steroid-pretreated patients, rebiopsy is recommended when close and careful follow-up with serial MRI indicates further tumor growth (Good Practice Point).
- PCNSL are diagnosed according to the WHO classification. Immunohistochemistry is required (Good Practice Point, see pathology section in the webappendix).
- Required immunohistochemical markers for the lymphoma cell characterization should include: pan-B cell markers (CD19,CD20,PAX5), BCL6, MUM1/IRF4, CD10 (Good Practice Point).
- PCR analysis of immunoglobuline gene families may contribute to diagnosis in difficult cases, in particular when inflammatory disorders such as multiple sclerosis or corticosteroid-mitigated PCNSL are considered. (Good Practice Point).
- In case of a suspicion of PCNSL, the work-up should include at least an HIV blood test, a lumbar puncture (if not contraindicated) and an ophthalmologic evaluation (with a fundoscopy and a slit lamp examination) in all patients, including those without ocular symptoms (Good Practice Point).
- The identification of lymphoma cells in the CSF or the vitreous may obviate the need for a stereotactic brain biopsy to confirm the diagnosis only in the setting of high clinical and radiological suspicion of PCNSL. As cytologic diagnosis may be difficult, a review by a specialist pathologist is recommended, and in any doubt a brain biopsy is required (Good Practice Point).
- Immunophenotyping by multiparameter flow cytometry of cells collected in the CSF or vitreous and immediately analyzed may add to diagnostic sensitivity.
- if B-cell monoclonality is shown in a sample with atypical/suspicious cells. PCR based analysis of immunoglobulin gene rearrangement in the CSF reportedly may show false positives. Therefore, evidence for the clonality of the lymphocytic cell population considered separately remains insufficient for the diagnosis for PCNSL except in case of high clinically documented suspicion of PCNSL (Good Practice Point).

Staging

- Systemic staging should include: physical examination, CT-scan of the chest, abdomen and pelvis, testicular sonography and bone marrow biopsy. FDG body PET may represent an improved alternative to total body CT-scan and testicular sonography (Good Practice Point).

Prognosis

- Age and performance status have been consistently identified as treatment-independent prognostic factors in PCNSL. Evaluating the individual risk of a PCNSL patient before treatment according to one of the existing prognostic scores is recommended (Good Practice Point).
- Age over 60-65 is used to define the elderly population in PCNSL (Good Practice Point).

Evaluation of response and follow-up

- The International Primary CNS Lymphoma Collaborative Group (IPCG) criteria (2005) combining MRI, eye examination, CSF analysis and steroid dose should be used to evaluate response to treatment (Good Practice Point).
- There is no evidence as yet that brain FDG PET can be used to assess response in PCNSL in the way that it is used for other lymphomas (Good Practice Point).
- Formal prospective neuropsychometric testing is recommended in the follow-up of patients treated in clinical trials on PCNSL (Good Practice Point).

Table 2: Consensus statements and recommendations for treatment of patients with PCNSL

Surgery

- Surgical resection may be considered in patients suffering from a large space occupying lesion with acute symptoms of brain herniation to reduce rapidly intracranial pressure (Good practice point).
- In patients with an unifocal and resectable lesion suspected of PCNSL, no consensus was met in the panel to recommend either surgical resection or biopsy

Chemotherapy

- CHOP-regimens and derivatives are not indicated in PCNSL (Level B).
- Chemotherapy should include MTX at HD ($\geq 3\text{g/m}^2$) both to cross the BBB and yield cytotoxic levels in the CSF. It should be delivered in 2-3 hour iv infusions for a minimum of 4-6 injections and at intervals that should not exceed 2-3 weeks (Good Practice Point).
- Combination of HD-MTX with other chemotherapeutic agents improves the response rates with respect to HD-MTX alone (Level B).
- Chemotherapeutic agents to combine with HD MTX should be selected among active drugs known to cross BBB, such as HD cytarabine (Level B).
- HD-MTX-chemotherapy is feasible in elderly patients with adequate performance status and renal function (Level B).
- BBBD followed by IA MTX is an alternative experimental approach appropriated for a selected group of patients that should be undertaken by trained teams only (Level B).
- The value of IT chemotherapy as prophylaxis is unclear. IT chemotherapy (intralumbar or preferably intraventricular through an Ommaya reservoir) can be proposed in case of documented meningeal involvement with insufficient response to iv HD MTX ($>3\text{g/m}^2$) based chemotherapy (Good Practice Point).
- Rituximab combined with a chemotherapy regimen is still an experimental regimen that has its main place in clinical trials (Level C).

Radiotherapy

- WBRT, HD MTX, and *a fortiori* combined treatment expose patients to an increased risk of neurotoxicity (Level A).
- The role of consolidation WBRT following HD-MTX based chemotherapy remains debated. In addition, the optimal dose is not yet defined, but it should be chosen on the base of response to primary chemotherapy (Good Practice Point).
- In patients with progressive or residual disease after primary chemotherapy, a total dose of 40-45 Gy with a 1.8-2 Gy dose /fraction appears advisable. With such doses, there is no evidence to add a focal boost on the enhancing lesions (Good Practice Point).
- In patients < 60 years who have achieved a CR to induction chemotherapy, the option of immediate WBRT (40 - 45 Gy in 1.8 - 2.0 Gy fractions) or WBRT omission should be discussed with the patient. Reduced dose WBRT consolidation (23.4 - 30 Gy in 1.8 - 2.0 Gy fractions) is a therapeutic option that should be investigated in a clinical trial (Good Practice Point).
- In patients > 60 years, the risk of delayed neurotoxicity, after WBRT (doses >30 Gy in 1.8-2.0 Gy fractions) especially if following HDMTX , is unacceptably high and WBRT at this dose should be deferred or avoided (Level B).

High dose chemotherapy with autologous stem cell transplantation (HDC/ASCT)

- HDC/ASCT is an efficient treatment in relapsed or refractory PCNSL (Level B).
- HDC/ASCT should be reserved for patients < 60-65 years (Good Practice Point).
- High-dose thiotepa-based conditioning chemotherapy should be preferred over the BEAM regimen (Level C).
- HDC/ASCT as consolidation in first-line treatment remains experimental in PCNSL and should be restricted by selected trained centers (Good Practice Point).

Primary intraocular lymphoma (PIOL)

- PIOL may be treated by either HD-MTX-based chemotherapy (with or without WBRT) or by local therapy (intravitreal chemotherapy or ocular RT) (Good Practice Point).
- Local treatment (intravitreal chemotherapy or ocular RT) is a valid approach for patients with systemic chemotherapy contraindications or for elderly patients with relapsing intraocular disease (Good Practice Point).
- Concurrent intraocular and CNS lymphoma should be treated no differently from PCNSL (Good Practice Point).
- If consolidation WBRT is proposed, it should include both eyes (Good Practice Point).

- Refractory and relapsed IOL should be treated according to the patients' characteristics and prior treatments. Treatments include intravitreal injections of MTX, focal radiotherapy, WBRT, systemic chemotherapy and HDC/ASCT (Good Practice Point).

Salvage treatment

- Patients with relapsed / refractory PCNSL should be enrolled into phase I-II trials (Good Practice Point).
- The choice of the most appropriate salvage treatment should depend upon the patient's age, performance status, comorbidity, site of relapse, prior therapy, and duration of previous response. The expected side effects of the chosen drug must also be considered carefully (Good Practice Point).
- Salvage WBRT may be proposed in radiotherapy-naïve patients; it may be preceded by induction chemotherapy (Good Practice Point)
- HDC/ASCT is a valid therapeutic option in patients aged <60-65 years with chemosensitive relapsing PCNSL (Level B).
- Salvage chemotherapy can be delivered as induction therapy before WBRT or HDC/ASCT, or as exclusive treatment in patients not eligible for these therapies.
- MTX re-challenge should be considered in recurrent PCNSL patients who previously responded to HD MTX (Level C).
- Isolated extra-CNS relapses should be managed with anthracycline-based chemotherapy followed or not by HDC/ASCT (Good Practice Point)

WEBAPPENDIX

This webappendix summarizes evidences used for EANO's recommendations for the general approach to PCNSL patients with coverage of diagnostic aspects – pathology and genetics, clinical presentation, pathological confirmation, neuropathology of corticosteroid-treated PCNSL, cerebrospinal fluid (CSF) analyses, vitreous analyses, staging, – as well as prognostic factors, response criteria to treatment, treatment related neurotoxicity and treatment of intraocular lymphoma.

Pathology and genetics

PCNSL is a mature B cell lymphoma corresponding to DLBCL of the CNS. Morphologically, haematopoietic tumor cells, mostly resembling centroblasts, are scattered throughout the brain tissue and also exhibit a marked angiotropism with sheets of tumor cells clustering within and around blood vessel wall. Immunohistochemistry is required for the diagnosis. In addition to the expression of pan-B cell markers (CD19, CD20, PAX5), the tumor cells of PCNSL are characterized by a BCL6⁺IRF/MUM1+CD10⁺ immunophenotype with high proliferative activity (Ki-67 indexes of 70-90%), together with high expression of the MYC and BCL2 proteins.¹⁻³ With rare exception, Epstein-Barr Virus (EBV) is absent from PCNSL of immunocompetent patients. Ongoing activity of the germinal center program and blocked terminal B cell differentiation together with pathways deregulated by genetic alterations (B cell receptor, toll like receptor, NF-κB pathways) may foster B cell activation and brisk proliferation and be of pathogenetic relevance.⁴⁻⁹ Analysis of the molecular landscape of PCNSL indicates that aberrant somatic hypermutation which targets several genes (*PIMI1*, *TTF*, *MYC*, *KLH14*, *OSPL10*, *SUSD2*) may play an important role in the pathogenesis of PCNSL,^{9,10} and that alterations in genes of role in CNS development may facilitate DLBCL manifestation in the CNS.¹⁰ Epigenetic studies revealed frequent gene silencing due to CpG island hypermethylation in individual genes including *MGMT*, *CDKN2A*, and *DAPK*.^{11,12} Recurring chromosomal losses affected the 6q, 6p21.32 (*HLA* locus) and 9p21 (*CDKN2A* locus) regions.^{5,13} However, to date, no specific molecular genetic signature distinguishes clearly PCNSL from non-CNS DLBCL, suggesting an important role of the microenvironment in explaining the peculiar behaviour of PCNSL. For research, collecting frozen samples and developing a network for PCNSL tumor banks should be encouraged.

Diagnosis

Clinical presentation

Presenting symptoms may include cognitive decline and/or personality changes, focal neurological deficits and increased intracranial pressure. Seizures are less frequent (10%). Ocular symptoms, due to an involvement of retina, choroid or vitreous, are represented by floaters and/or blurred vision; they can be either isolated (10%) or coexist with cerebral symptoms (10-20%). However, up to one-half of patients with PCNSL and ocular involvement have no visual symptoms. Insidious onset and delayed diagnosis of intraocular lymphoma are common.¹⁴ In immunocompetent patients, cranial MRI with contrast enhancement typically shows intense and homogeneously enhancing single lesions (70%) or multiple lesions (30%) with modest surrounding edema, usually located in periventricular areas and/or deep gray matter.^{15,16} Although suggestive, all these MRI findings are not specific. Advanced imaging techniques, especially FDG-PET, diffusion tensor imaging, dynamic susceptibility contrast MRI (DSC-MRI) and proton MR spectroscopy can increase the diagnostic accuracy and help in differentiating PCNSL from other brain tumors or non-tumor lesions.¹⁷⁻²⁶ However, although some signatures are highly suggestive of PCNSL, especially when present together (low regional cerebral blood volume ratios, high percentage of signal-intensity recovery at the end of the first pass of contrast agent relative to baseline, very high lipid resonances), they are not sufficiently specific in practice to replace pathological confirmation.

Pathological confirmation

Diagnosis always needs to be confirmed pathologically, according to the WHO classification in most cases by stereotactic needle biopsy.¹ In classical cases, combined histology and immunohistochemistry yields the diagnosis of PCNSL, i.e. DLBCL of the CNS. In such cases, molecular studies are not required. In equivocal cases PCR testing for clonality may aid the diagnosis.^{27,28}

Neuropathology of corticosteroid-treated PCNSL

As the tumor cells of PCNSL are potentially highly sensitive to corticosteroids, they may undergo rapid apoptosis. Transient tumor shrinkage or disappearance of contrast enhancement may occur even after short

exposure to steroids in approximately 40% of PCNSL, coupled with significant neurological improvement.²⁹ Stereotactic or navigation guided needle biopsy in this setting may be non-diagnostic in up to 50% of cases.³⁰ In the absence of tumor blasts, resorptive changes with prominent infiltration of macrophages, T cells, reactive astrocytes, and prominent microglial activation may prevail. In some cases, a few enlarged B cells may persist, being suspicious of blast. In such cases, PCR analysis of immunoglobulin genes may demonstrate monoclonality. However, a small number of B cells may pretend monoclonality ("pseudoclonality"). Therefore, unless patients are rapidly deteriorating with suggestive radiological features of PCNSL, it is usually recommended to defer corticosteroids until histologic confirmation has been obtained. Clinicians referring from peripheral hospitals should discuss with the specialist neurosurgical centre before starting corticosteroids. If, nevertheless, corticosteroids have been given with a subsequent objective response, tapering corticosteroids within one or two weeks and delaying biopsy until tumor regrowth would be a reasonable option. Since regrowth occurs in most cases within a few weeks after discontinuation corticosteroids, a serial MRI follow-up with one month interval may be recommended at least the first three months. If no significant changes in contrast enhancement or progression are observed, biopsy seems associated with a relatively good probability of yielding a diagnosis despite steroid pre-treatment.³¹

CSF analysis

The identification of lymphoma cells in the CSF or in a vitreous biopsy, when possible, may obviate the need for a brain biopsy for the diagnostic confirmation, only in the setting of high clinical and radiological suspicion of PCNSL. Frequently, CSF is characterized by elevated protein levels in 75% and mild pleiocytosis in 50% of patients. However, lymphoma cells are detected in only 10-30% in the CSF.^{32,33} Cellular immunophenotyping by flow cytometry in the CSF and PCR analysis of immunoglobulin heavy and light chain genes may help to distinguish malignant cells from reactive lymphocytes by identifying clonal B-cell populations even when cytological examination is negative.^{34,35} However, low cell numbers in the CSF sample are frequently found and may make flow cytometric analysis difficult. A relatively high ratio of PCR false negatives has been reported in PCNSL.^{33,36} Different CSF molecular genetic markers and proteins including microRNA (miR-21, miR-19b, and miR-92),³⁷ soluble CD19,³⁸ antithrombin III,³⁹ free immunoglobulin light chains,⁴⁰ and interleukin-10 and CXCL13,⁴¹ are potentially useful diagnostic biomarkers for PCNSL but require further validation before being used in routine practice. As cytologic diagnosis may be difficult, in any doubt or inconsistencies with the patient clinical setting, a pathological confirmation by a brain biopsy is recommended.

Vitreous analysis

Ophthalmologic evaluation includes fundoscopy and slit lamp examination. Fluorescein angiography may be useful for lymphomatous involvement of the retina.¹⁴ Ophthalmologic involvement has to be confirmed by vitreous biopsy when eyes are the unique site of disease. Positive cytology is obtained in 70% of cases in trained pathology department. As for CSF, immunophenotyping and detection of IgH or T-cell receptor rearrangements by PCR analysis indicating monoclonality are helpful tools for diagnosis.^{42,43} High levels of interleukin 10 (IL10) and/or high IL10 / IL6 ratio in ocular fluids are strongly suggestive of B-cell lymphomatous uveitis,⁴⁴ but are not diagnostic.

Staging

The aims of staging are both to specify the extent of the lymphoma within the CNS and to exclude the presence of the disease elsewhere. If not contraindicated and already performed at the diagnostic work-up, all patients should have a lumbar puncture for CSF cytology. Systemic involvement is present in up to 12% of the cases.^{45,46} Since identification of a systemic site of the lymphoma has important implications for the treatment strategy, an international workshop to standardize baseline evaluation recommended performing at least a CT-scan of the chest, abdomen and pelvis, a bone marrow biopsy, a testicular ultrasound in elderly males.⁴⁷ FDG body PET, which is more sensitive than the body CT-scan,⁴⁸ is not yet an established routine diagnostic investigation, but is used in some European countries as an integral part of diagnostic work-up.

Prognostic factors

Age and performance status have been consistently recognized as the most important therapy-independent prognostic factors.⁴⁹⁻⁵³ Based on retrospective cohorts of PCNSL, other variables including serum lactate dehydrogenase (LDH) levels, involvement of deep brain structures,⁵³⁻⁵⁵ CSF protein levels,^{50,53} and extent of lesions within the CNS (multifocal versus unifocal),⁵² have been correlated with outcome, and some of them are integrated with age and performance status in different prognostic scoring systems. Hence, three clinically meaningful prognostic scores are available for PCNSL: the IELSG score,⁵³ the MSKCC score,⁵¹ and the Nottingham-Barcelona score.⁵² All of them distinguished 3 different risk groups. Using such scoring systems is useful to compare studies in order to avoid as much as possible selection biases. Since then, other prognostic

factors have been correlated with unfavorable outcome and need to be validated in independent series: elevated FDG uptake on PET,⁵⁶ chromosome 6q deletion or *CDKN2A* homozygous deletion in the tumor DNA,^{5,57} and delayed response to initial chemotherapy, as compared to early response.⁵⁸ Several variables have yielded opposite results in retrospective studies, such as apparent diffusion coefficient (ADC) value derived from diffusion-weighted imaging,⁵⁹⁻⁶¹ BCL-6 expression analysis,⁶²⁻⁶⁶ and MTX exposure reflected by MTX area under the curve (AUC).⁶⁷⁻⁷⁰

Response criteria

In 2005 the International Primary CNS Lymphoma Collaborative Group (IPCG) published a consensus opinion to standardize response criteria and outcome measures in immunocompetent patients with PCNSL.⁴⁷ These response criteria define CR as complete disappearance of contrast enhancement on MRI, no evidence of ocular lymphoma, negative CSF cytology and discontinuation of corticosteroid use for at least 2 weeks prior to the evaluation of response. Since corticosteroids may mask presence of residual disease its discontinuation is included as an essential requirement. The IPCG also delineated which findings are compatible with unconfirmed CR (CRu). It is important to sort out CRu from PR because the latter means failure of primary treatment. According to the IPCG outline CRu includes those cases who fulfill the criteria for CR with the following limitations: at time of evaluation the patient is still on any dose of corticosteroids, MRI continues to show small but persistent enhancing abnormalities related to biopsy/surgical site or to focal hemorrhage, and the follow-up ophthalmologic examination shows persistent minor abnormality which is unlikely to represent ocular lymphoma. PR is defined as 50% decrease in enhancing tumor or residual disease on eye examinations, or persistent or suspicious CSF cytology. Progressive disease (PD) is recognized as 25% increase in the enhancing lesion or appearance of any new site of disease in the CNS or as systemic disease, recurrent or new ocular disease, or recurrent or positive CSF cytology. Of note, these definitions do not take into account the non-enhancing lesion best visualized on T2-Flair MRI, whose differential diagnosis may be challenging since it could be treatment-related white matter changes (including leukoencephalopathy) but also correspond to infiltrative PD.⁷¹ There is no evidence as yet that brain FDG PET can be used to assess response in PCNSL in the way that it is used for other lymphomas.

Delayed neurotoxicity

Delayed treatment-related neurotoxicity has been systematically evaluated in few studies (Class II and III). However, there is a general perception and agreement, that the combination of HD MTX and WBRT is associated with disabling neurotoxicity with an incidence of 25% to 35% and related mortality of 30%.^{50,72} This deleterious treatment complication typically occurs several months to years after successful treatment. Neuropsychological examination may confirm impaired psychomotor speed, executive function, attention and memory.⁷³ Affected patients show cortical/subcortical atrophy and leukoencephalopathy,⁷³⁻⁷⁵ which may leave them demented, ataxic and incontinent. Median survival after onset of clinically-evident neurotoxicity is less than 1-2 years.^{50,72,75} Autopsy findings include myelin and axonal loss, gliosis, spongiosis, thinning of white matter, small and large vessel disease, and necrosis.^{75,76} Of note, imaging abnormalities may not always correlate with the neurologic impairment severity over time. In a retrospective mono-institutional series analysis of 183 patients, only the administration of WBRT was identified as an independent risk factor for the development of late neurotoxicity: in this series, 2% treated with chemotherapy alone developed clinically-evident neurotoxicity, while 33% treated with combination chemo-/radiotherapy were affected. The cumulative incidence of neurotoxicity for the whole group was 5% at 2 years and 24% at 5 years, with a substantially higher risk in patients ≥ 60 years (Class IIb).⁷⁵ They are related to clinically and radiologically overt neurotoxicity. The prevalence of treatment-related “subtle” cognitive dysfunction amongst patients treated for PCNSL is probably largely underestimated as formal psychometric evaluations have not been routinely performed in most prospective studies. Small case series identified WBRT, and not chemotherapy, as the primary cause of neurotoxicity in PCNSL.^{76,77} These results have been confirmed by 3 long-term evaluations (Class IIb).⁷⁸⁻⁸⁰ In the most recent analysis of 80 long-term survivors of PCNSL, free of tumor and having completed treatment with different regimens at least two years prior to evaluation, those who had received WBRT showed significantly lower mean scores in attention and executive function, motor skills, and neuropsychological composite score, associated with poorer quality of life measures (Class IIb).⁸⁰ Moreover, on brain imaging, mean areas of total T2 abnormalities in the WBRT group were more than twice the mean of any other non-WBRT group. These results caution against the routine administration of WBRT as part of upfront treatment and call for the implementation of formal neuropsychometric testing in clinical trials on PCNSL.⁷³

Intraocular lymphoma

Intraocular infiltration can be the exclusive site of disease at presentation, the so-called primary intra-ocular lymphoma (PIOL), or as a part of PCNSL with concomitant brain or meningeal disease. The optimal treatment for intraocular lymphoma is not known. Data on therapy and outcome are scarce and limited to retrospective case reports or mostly small series with heterogeneous patient populations and treatments. As many as 90 % of patients with PIOL patients consequently develop brain involvement over the course of the disease and dissemination to the brain is the main cause of death.^{14,81} The median survival of isolated PIOL is approximately 60 months.^{81,82} Treatment may be focal, including ocular RT (historically, total dose of 35-40 Gy, 2 Gy per fraction using opposed lateral beams to include both globes) (Class IV) and intravitreal chemotherapy.⁸³⁻⁸⁶ Uncontrolled series have reported clinical remission with repeated intravitreal MTX and more recently after rituximab injections (Class IV).^{85,86} Treatment may be also extensive, including systemic chemotherapy and WBRT. Intraocular responses have been reported with HD MTX,⁸⁷ HD cytarabine,^{88,89} ifosfamide, trofosfamide used as single agent,⁹⁰ with MTX-based polychemotherapy and after HDC/ASCT (Class IV).⁹¹ A large retrospective multicenter study did not show any difference in PIOL between focal and extensive therapy in terms of disease control and survival (Class IIb).⁸¹ Unfortunately, this and other studies failed to provide reliable predictors of brain dissemination in PIOL patients; thus, some experts recommend local therapy for disease confined to the eyes, but others consider that initial treatment of PIOL should not differ from that of PCNSL i.e. high-dose MTX-based polychemotherapy followed, or not, by WBRT in order to eradicate possible concomitant microscopic disease in the brain and in the CSF responsible for relapse. In this case, local treatments would remain options for refractory or recurrent disease confined to the eyes. The management decision should take into account the individual risk of treatment toxicities (including those related to ocular treatment) and local expertise.^{14,92} When intraocular lymphoma is concurrent with brain lesions, it has not been identified as an independent prognostic factor and the prognosis is similar to that of the PCNSL without intraocular disease (Class IIb).⁹³ Accordingly, patients with concomitant intraocular and cerebral disease should be treated no differently from PCNSL. The value of additional local ocular treatment (i.e. intravitreal chemotherapy or ocular radiotherapy if WBRT has not been delivered) to systemic chemotherapy remains matter of debate, with conflicting results in two retrospective studies (Class IIb).^{93,94}

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EANO Guideline for the diagnosis and treatment of primary CNS lymphoma in immunocompetent patients.

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Abstract

The management of primary central nervous system (PCNSL) is one of the most controversial topics in neuro-oncology because of the complexity of the disease and the very limited number of controlled studies available. In 2013, the European Association of Neuro-Oncology (EANO) created a multidisciplinary task force to establish evidence-based guidelines for immunocompetent adult patients with PCNSL. The guideline provides consensus considerations and recommendations for diagnosis, staging and treatment of PCNSL, including surgery, systemic and intrathecal chemotherapy, intensive chemotherapy with autologous stem cell transplantation, radiotherapy, intraocular manifestations, and specific management of elderly patients. The guideline should aid the clinicians in everyday practice and decision making and serve as a basis for future research in the field.

Introduction

Primary central nervous system lymphomas (PCNSL) are extranodal malignant non-Hodgkin lymphomas (NHL) of the diffuse large B cell (DLBCL) type confined to the brain, eyes, leptomeninges, or spinal cord in the absence of systemic lymphoma. Currently PCNSL are estimated to account for up to 1% of lymphomas, 4-6% of all extranodal lymphomas, and about 3% of all CNS tumors.¹ After a continuous increase in the 1980's and 1990's, epidemiologic data in Western countries show a decrease in the incidence of PCNSL, particularly among young patients suffering from AIDS.² In contrast, the incidence continues intriguingly to rise in the elderly who represent consequently the large majority of patients in the immunocompetent population in some recent studies.³⁻⁵ Although the prognosis of PCNSL remains poor, it has significantly improved over the past two decades as a result of better treatment strategies with a curative aim. Treatment of PCNSL is challenging. Despite a high chemosensitivity and radiosensitivity, remissions are frequently short-lasting; the blood brain-barrier (BBB) limits the access of many drugs to the CNS; and patients, especially the elderly, are at high risk of developing severe treatment related-neurotoxicity. To date, therapeutic knowledge to define the optimal treatment mainly results from retrospective series or single arm phase II studies, with only three completed randomized trials available: one phase III and two phase II. The objective of this guideline is to provide clinicians with evidence-based recommendations and consensus expert opinions on the management of patients with PCNSL. The present guideline focuses on the immunocompetent population which represents the vast majority of the patients today. PCNSL of immunodeficient patients and the rare indolent low grade lymphomas occurring primarily in the CNS, which have a distinct pathogenesis with separate diagnostic and therapeutic implications, will be subject to specific guidelines.

Search strategy and selection criteria

The guideline task force was set up in 2013 under the auspices of the EANO (European Association for Neuro-Oncology) and selected to be representative of European-based medical experts (10 countries). The panel covered all fields of expertise in the management of PCNSL, i.e. neurologists, haematologists, medical oncologists, neurosurgeons, pathologists, ophthalmologists and radiation oncologists. Based on best available evidence from literature review, the writing group (EB, JB, AH, KHX, MP, RR, US, TS, CS) produced the draft guideline, which was subsequently submitted to the review committee (UA, NC, MD, CD, AF, FG, RH, UH, RS, MT, MW). The revised guideline, taking into account the comments of the reviewers, was resubmitted by the chairman to the whole task force for review and amendments twice. Thereafter, final agreement was obtained in September 2014. When

analyzing results and drawing recommendations, at any stage, differences were resolved by discussion and, if persisting, were reported in the text. References for this review were identified through searches of PubMed with the search terms "primary CNS lymphoma", "primary central nervous system lymphoma", "primary intraocular lymphoma", "elderly", "radiotherapy", "chemotherapy" and "rituximab" from January 1980 to September 2014. Articles were also identified through searches of the authors' own files. The final reference list was generated on the basis of originality and relevance to the broad scope of this review. Abstracts presented at the annual ASCO meeting in 2013 and 2014 relevant to the topic were included by task force members during manuscript preparation. The scientific evidence of papers collected from the literature was evaluated and graded as follows and recommendations were given accordingly. Class I evidence was derived from prospective, randomized, phase III clinical trials; class IIa evidence was derived from prospective randomized phase II trials, class IIb evidence was derived from phase II trials; class IIIa was derived from prospective studies, including observational studies, cohort studies and case-control studies; class IIIb evidence was derived from retrospective studies; class IV evidence was derived from uncontrolled case series, case reports and expert opinion. As for recommendations, level A required at least one class I study or two consistent class IIa studies, level B at least one class IIa study or overwhelming class IIb and III evidence and level C at least two consistent class III studies. Pathology, genetics, clinical features and neuroimaging were simply reviewed but not graded. When sufficient evidence for recommendations A–C was not available, we gave a recommendation as a "Good Practice Point", if agreed by all members of the Task Force.

General recommendations

Consensus statements and recommendations for the general approach to patients with PCNSL, including: 1/ pathology and genetics, 2/ clinical presentation, 3/ diagnostic confirmation, 4/ neuropathology of corticosteroid-treated PCNSL, 5/ neuroimaging, 6/ cerebrospinal fluid (CSF) analyses, 7/ vitreous analyses, 8/ staging, 9/ prognostic factors, 10/ response criteria to treatment, and 11/ treatment-related neurotoxicity are presented in table 1. The evidences used to establish these recommendations are detailed in the supplementary webappendix. Key recommendations for treatment are summarized in table 2. The evidences concerning intraocular lymphoma are presented in the webappendix. Our guideline covers treatment of histologically or cytologically proven PCNSL. We have not covered specifically the treatment of patients with deep seated tumours not readily amenable to biopsy for which there are no evidence-based recommendations. We believe that biopsies are almost always possible in specialized centers and that chemotherapy and/or radiotherapy interventions without histological confirmation of PCNSL should be discouraged.

Surgery

Although very few data are available in the literature, surgery has traditionally been considered to have no role in the treatment of PCNSL. This widely adopted opinion is based on small retrospective series suggesting no clear benefit in outcome of surgical resection used as sole treatment compared with supportive care (Class IIb),⁶ and compared with biopsy in patients having received post-operative chemotherapy and/or radiotherapy (Class IIb).^{7,8} This may be explained by the microscopically multifocal and infiltrative nature of PCNSL that may extend beyond the visible border of the lesion.⁹ The relative radiosensitivity and high chemosensitivity of PCNSL, and the increased risks of postoperative morbidity of this patient population have also contributed to discourage surgery. However, the recommendation to restrict surgical interventions to biopsies is not based on randomized data and, more importantly, not on contemporary data reflecting modern neurosurgery. The German PCNSL Study Group-1 phase III trial included an unusually high rate of operated patients, which allowed the largest and most recent retrospective analysis of an association of surgery and outcome. A significantly longer progression free survival (PFS) and overall survival (OS) in patients with subtotal or gross total resections compared with biopsied patients was reported. This difference in outcome was independent of post-operative Karnofsky performance status (KPS) and age. Since biopsied patients more often had multiple and/or deeply seated CNS lesions than resected patients, these features may have contributed to the unfavourable outcome. When adjusted for the number of lesions (site of the lesions was not analyzed in the study), the difference in outcome remained significant in term of PFS but did not reach the significance threshold for OS (Class IIIa).¹⁰

Systemic chemotherapy

The CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) regimen commonly used for systemic NHL induces short-lasting responses in PCNSL and its addition to radiotherapy has not shown a survival benefit in prospective trials (Class IIb).¹¹⁻¹³ This inefficacy is probably due to the fact that phosphoramidate mustard and doxorubicin are not able to cross the blood-brain barrier (BBB) to eradicate microscopic disease. Based on convergent results from numerous prospective and retrospective studies, high-dose (HD) intravenous (iv) methotrexate (MTX), an antifolate and antimetabolite, is now considered the most important and beneficial single agent. Penetration of MTX into the CNS depends both on the total dose and rate of infusion. The optimal dose of MTX has not been determined. It has been estimated that the iv MTX should range between 1 g/m² and 8 g/m² to cross the BBB. In the absence of clear evidence for dose-response relationship, and since rapid infusion of MTX $\geq 3\text{g/m}^2$ over 3 hours achieves cytotoxic levels in the CSF, there is a growing consensus to deliver MTX according to this protocol (Class IV).¹⁴ Since efficacy of MTX may also depend on duration of exposure, MTX administration interval should range between 10 days and 3 weeks (Class IV).¹⁵ The optimal number of MTX injections to deliver is unknown. A minimum of 4-6

injections is delivered in most chemotherapy regimens, especially if no consolidation treatment (radiotherapy and/or intensive chemotherapy) is scheduled in the protocol. For patients who achieved only partial response (PR) after 4-5 courses of HD MTX, additional courses may improve the complete remission rate (Class IIIa).¹⁶ Infusions of HD MTX require pre- and post-hyperhydration, urine alkalinization, leucovorin rescue and MTX concentration monitoring. Currently most treatment protocols combine HD MTX with a variety of other chemotherapeutic agents to improve response rate and outcome. The best evidence to support this approach comes from an IELSG randomized phase II study comparing HD MTX alone, administered at 3 g/m²/d every 21 days, to HD MTX with cytarabine (2 g/m² twice per day on days 2–3)(Class IIa).¹⁷ Both chemotherapy arms were followed by WBRT. This study showed a significantly higher complete response (CR) rate in the HD MTX-cytarabine arm. Regarding secondary endpoints, a significantly improved overall response rate (ORR), PFS and a trend towards better OS in the HD MTX-cytarabine arm were noticed. Two previous prospective trials evaluating HD MTX at a dose of 8g/m² as single agent and without immediate consolidation WBRT resulted in a shorter PFS when compared to polychemotherapy regimens (Class IIb).^{18,19} Similarly, the addition of ifosfamide to HD-MTX improved response rate, but not survival, in the G-PCNSL-SG-1 trial.²⁰ Altogether, these data resulted in the recognition that only HD MTX can be defined as a chemotherapy standard of care.²¹ Chemotherapeutic agents to be combined with HD MTX should be selected among active drugs known to cross the BBB, such as HD cytarabine. Recently, the CALGB50202 multicenter phase II trial reported promising results using HD cytarabine combined with etoposide as consolidation without WBRT following a HD MTX-based polychemotherapy as induction regimen (Class IIb).²² In contrast, very disappointing results have been reported in a pilot study combining HD MTX (3.5g/m²), thiotepa and cytarabine at a reduced dose of 1g/m² suggesting that the cytarabine dose probably was suboptimal to reach cytotoxic levels in the CNS (Class IIIa),²³ as supported by pharmacokinetic studies.²⁴ Another approach is BBB disruption (BBBD) by intra-arterial (IA) infusion of hypertonic mannitol followed by intra-arterial (IA) chemotherapy to increase the drug concentration in the CNS. BBBD with IA MTX administered in newly diagnosed PCNSL demonstrated a good safety profile and neurocognitive tolerance and achieved comparable outcomes to those observed with HD-intravenous MTX based chemotherapy regimens (Class IIIb).²⁵⁻²⁷ However, conversely to those reported in prospective studies on chemoradiotherapy, even after a follow-up longer than 10 years (Class IIb),²⁸ BBBD is not associated with a plateau in survival curves, suggesting a continuum of relapses and deaths. This procedure requires patient selection as safety depends on the extent of intracranial mass effect and the procedure is limited to patients with no contraindications for general anesthesia. It should be managed by teams trained in BBBD as it is complex, requiring cannulation of the intracranial vessels. In summary, HD MTX is the drug of choice for PCNSL. In patients who are not eligible for HD MTX, treatment should be chosen from treatments active as salvage in refractory or recurrent PCNSL after initial HD MTX based chemotherapy (see salvage treatment section).

Intrathecal chemotherapy

Intrathecal (IT) chemotherapy administration has not been prospectively studied and its efficacy in PCNSL remains debated. Three retrospective studies did not demonstrate benefit from the addition of intrathecal drugs (MTX, cytarabine) in patients treated with HD MTX dosed at 3g/m^2 (Class IIb).²⁹⁻³¹ In contrast, two consecutive single arm trials using the same systemic polychemotherapy regimen suggested additional benefit when intraventricular chemotherapy was added (Class IIIa).^{32,33} However, given the low level of evidence, we currently do not advocate IT chemotherapy as prophylaxis.

Rituximab

Based on its poor penetration into the CNS related to its large size, the maximal concentration and efficacy of the anti-CD20 antibody rituximab in the CNS might be assumed to occur in the early treatment phase, during BBB breakdown within the tumors. The effect of rituximab when used as monotherapy in PCNSL was evaluated in a single study in which 12 patients with refractory or relapsed PCNSL were treated with a weekly iv dose of 375 mg/m^2 rituximab infusion for up to eight doses (Class IV).³⁴ MRI responses were observed in 36% of patients. Other studies used iv rituximab in combination with a HD MTX-based chemotherapy regimen as initial treatment for newly-diagnosed PCNSL or as salvage treatment for recurrent PCNSL (Class IIIa, Class IIb and IV).^{16,22,35-41} Three studies suggested that the addition of rituximab to HD MTX-based chemotherapy improves the CR and OS rate in patients with newly-diagnosed PCNSL based on retrospective comparison with historical controls (Class IIb).³⁹⁻⁴¹ Overall, the addition of rituximab to systemic polychemotherapy is well tolerated. Injection of rituximab into the CSF via either lumbar puncture or by intraventricular administration was evaluated in phase I for refractory or recurrent CNS lymphoma patients (Class IIIa).⁴² In these studies objective responses and good tolerability were documented confirming small case series. In conclusion, the existing level of evidence supporting either systemic or local use of rituximab as part of treatment protocol for PCNSL remains low. Yet, the preliminarily available information suggests that it may add some benefit. Two ongoing randomized trials (NCT01011920; NTR2427) should clarify the role of systemic rituximab in PCNSL.

Radiotherapy

Because of the microscopically diffuse and multifocal nature of PCNSL, radiotherapy (RT) has so far involved the whole brain, including the eyes. Despite a high response rate in the range of 50%, RT used as sole treatment modality, provides limited survival benefit in PCNSL patients, with a median OS duration of 10–18 months and a 5-year survival rate of 5%. The only phase II trial, conducted by

the RTOG, which delivered a total dose of 40 Gy with an additional 20-Gy boost to contrast-enhancing lesions, reported a disappointing 11.6 month OS (Class IIb).⁴³ In addition, the majority of relapses occurred in fields that had received the highest RT dose. Although not formally compared in a randomized trial, a wide consensus is shared which considers that HD MTX-chemoradiation is superior to RT-alone, allowing for a 2 to 4-fold increase in OS (median: 30-72 months) and long-term survivors (5-year survival of 20-50%) for many protocols (Class IIb, IIIa IIIb).^{15,44-52} In contrast to extracerebral NHL, the optimal dose of post-chemotherapy irradiation has never been prospectively investigated in PCNSL.⁵³ Doses of 23–50 Gy to the whole brain, with or without a tumor bed boost, are currently used, with most of the protocols delivering a total dose of 40–45 Gy without boost, and standard fractionation (1.8-2Gy/fraction). The RTOG-9310 trial did not show a clear benefit with hyperfractionated WBRT (Class IIb).⁵⁴ For patients who achieve a CR after HD MTX-based chemotherapy, it remains unclear whether consolidation with WBRT provides better disease control or survival. There has only been one randomized trial of radiotherapy versus watch-and-wait after chemotherapy for PCNSL. This study (G-PCNSL-SG 1) conducted in Germany was a non-inferiority phase III trial, in which patients received HD MTX 4g/m² iv every 14 days for 6 cycles with or without ifosfamide. Those patients who achieved a CR had been randomized initially between consolidating WBRT, 45 Gy in 30 fractions over 6 weeks or no further immediate treatment. Patients without a CR received HD cytarabine or WBRT. A total of 551 patients entered the study, but 318 patients were treated per-protocol. OS was similar in both arms. In the whole per-protocol population, the WBRT arm was associated with a trend (not significant) for better PFS, as compared with the no WBRT arm but with no significant difference in OS.²⁰ This trial (Class I), which is, to date, the largest one and only phase III trial in PCNSL has raised vigorous debate within the community.⁵⁵⁻⁵⁸ Several experts consider that the unmet primary endpoint for non-inferiority and the high rate of protocol violations prevent any conclusions being drawn from the trial and advocate keeping consolidation WBRT after HD MTX-based chemotherapy as the standard of care, whilst awaiting results from further, ongoing randomized trials; while others, acknowledging the methodological limitations of the study, consider nevertheless that the results contribute strongly to the accumulating retrospective literature suggesting that omission of WBRT from first-line treatment results in shorter PFS but does not compromise OS (Class IIIb).^{29,59,60} In addition, several single arm trials have suggested that chemotherapy alone, plus a deferred RT strategy may result in comparable OS with those reported for combined chemo-RT but with better neurocognitive preservation (Class IIb, IIIa, IIIb).^{19,25,26,32,61-63} Since withdrawing consolidation WBRT for patients with CR to chemotherapy remains controversial, especially in patients less than 60 years old who are at lower risk of developing neurotoxicity, reduced dose WBRT is another alternative approach. Conflicting results have been reported. A subset analysis from a phase II trial that included 25 patients aged <60 years who achieved a CR after initial chemotherapy and received either 45 Gy or 30.6 Gy as consolidation treatment showed a significantly higher recurrence rate and lower OS rate in the reduced-dose RT group (Class IIIb).⁶⁴ On the other

hand, in a retrospective study of 33 patients with PCNSL who achieved CR after MTX-containing chemotherapy and were referred to consolidation WBRT, total doses ≥ 40 Gy were not associated with improved disease control in comparison with a WBRT dose of 30-36 Gy (Class IIIb).⁶⁵ More recently, a phase II trial evaluating an immunochemoradiation regimen (R-MPVA) including rituximab and HD MTX-based polychemotherapy, the 31 CR patients were offered reduced dose WBRT (23 Gy in complete responders) with encouraging results both in term of survival and neurotoxicity (Class IIb).¹⁶ Based on these results, a randomized phase II study (RTOG-1114) comparing the R-MPV regimen with or without reduced-dose WBRT is currently ongoing (NCT01399372). In summary, the role of consolidation WBRT following HD-MTX based chemotherapy remains debated especially in patients in CR. In addition, the optimal dose has not been defined yet.

High-dose chemotherapy, myeloablative conditioning and autologous stem cell transplantation (HDC /ASCT)

HDC/ASCT is the standard treatment for chemosensitive relapsing systemic DLBCL. For patients with relapsed or refractory PCNSL, there is only one multicenter phase II trial evaluating HDC/ASCT, with TBC conditioning regimen (thiotepa, busulfan, cyclophosphamide). The CR rate was 60%, median PFS and OS were 41 and 58 months respectively for the 27 patients out of 43 who completed the full HDC/ASCT procedure. For the whole population of this trial, the intent-to-treat median PFS and OS times were 11 and 18 months respectively. The toxicity-related mortality was 7% (Class IIb).⁶⁶ An update of this study to which additional cases have been included, and an independent retrospective single center series confirmed the benefit of the TBC regimen followed by ASCT (Class IIIb).^{67,68} Experiences with other HDC regimens in this setting of patients are limited to a few cases, which prevent any conclusions being drawn. Because of its toxicity risks, the HDC/ASCT is likely to be proposed for younger patients (<60-65 years) with a good performance status, which makes it difficult to compare with other salvage treatments, including second-line conventional chemotherapy regimens and WBRT. The specific role of HDC/ASCT as consolidation in first-line treatment is difficult to evaluate since WBRT was administered after HDC/ASCT in early studies (Class IIb).^{69,70} The first study with HDC/ASCT without WBRT used the BEAM regimen (BCNU, etoposide, cytarabine, and melphalan) as conditioning and reported a disappointing median event-free survival of 9.3 months (Class IIIa).⁷¹ Subsequently, encouraging studies for which WBRT had been omitted at least in patients in CR after HDC/ASCT using HD thiotepa-based conditioning regimens have been reported (Class IIIb and IV).⁷²⁻⁷⁵ Taken together, although direct comparison between conditioning regimens applied is difficult, HD thiotepa-based conditioning regimens seem more efficient than BEAM-based regimens. In summary, HDC/ASCT represents an effective treatment option for selected refractory and relapsed PCNSL patients, but should be reserved to experienced centers. Superiority of the HDC/ASCT approach compared to standard combined chemo-radiotherapy as first line treatment

has not been proven and is currently under investigation in two ongoing trials (NCT00863460, NCT01011920).

Elderly patients

Definition of 'elderly' is not uniform. However, in the studies available which have evaluated prognostic factors, older ages (over 50 and over 60) were consistently correlated with worse outcome (see the section on prognostic factors in appendix). Furthermore, for chemoradiation-induced neurotoxicity age > 60 was found to be highly prognostic (see the section on neurotoxicity in appendix). Therefore, age of 60 has been used as cut-off to define the elderly population in most of the studies. Four prospective studies have been published on treatment of elderly patients with PCNSL (Class IIb),^{36,63,76,77} seven prospective studies on patients of all ages but reporting specifically on older patients (Class IIIa),^{11,12,32,43,52,54,78} and seven retrospective studies reporting on ≥ 15 patients (Class IIIb).⁷⁹⁻⁸⁵ As in younger patients, results in patients treated with steroids or CHOP/CHOD in addition to radiotherapy do not differ from results after radiotherapy only (Class IIb).^{11,12,43,77} In the RTOG phase II trial, the median survival was only 7.8 months.⁴³ After HD-MTX-based therapy, defined as dose of MTX $\geq 1 \text{ g/m}^2$ PFS in patients aged 60 or 65 and older is reported between 6 and 16 months and OS between 14 and 37 months (Class IIb and Class III) with OS in the majority of prospective studies under 2 years.^{32,36,52,54,63,73,78-85} Other than within retrospective studies no direct comparisons have been made between treatment with HD-MTX-based chemotherapy and radiotherapy in this age group.⁸¹ However, the impression from the single arm studies is that survival after chemotherapy is at least as good and probably better after HD MTX-based chemotherapy than after radiotherapy (Class IV). Formal comparisons of different HD MTX-based regimens have not been published but in a recently completed randomized phase II study, toxicity was identical, CR rate, median PFS and survival appeared better after MPV-A (MTX, procarbazine, vincristine, cytarabine) than after MTX and temozolomide though the difference was not significant (Class IIa).⁸⁶ Five prospective studies report on chemotherapy toxicity in patients aged over 60. With the exception of one study, in which an intensive multi-drug regimen was used and toxicity was exceedingly high in older patients,⁵² HD MTX-based chemotherapy up to 3.5 g/m^2 was well tolerated with 2-7% treatment-related mortality, less than 10% grade 3-4 nephrotoxicity and 7-10% of patients discontinuing treatment due to chemotherapy-associated toxicity, though MTX dose was reduced because of decreased renal function in 26-44% of patients.^{36,63,76,87} Retrospective studies substantiate this view. Thus, in general, older patients tolerate treatment with HD-MTX well when adequate supportive measures are used and renal function is accurately monitored.³ As discussed in the neurotoxicity section (appendix), risk of delayed leukoencephalopathy is particularly high in patients older than 60 years managed with chemoradiotherapy. For patients treated with HD-MTX-based chemotherapy without radiotherapy no studies reporting specifically on older patients are available, but reports including neuropsychological

assessment of patients of all ages show little or no cognitive decline compared with post-treatment evaluations (Class IIIb).^{61,88} Given the available data on acute and long-term toxicity of radiotherapy and chemotherapy in older patients with performance status KPS \geq 70, treatment with HD MTX-based chemotherapy with deferral or elimination of WBRT is the treatment of choice. In older patients in poor condition and in the very old (over 80) who both have a worse prognosis,⁸⁵ the acute morbidities and frequent admissions to hospital associated with HD-MTX chemotherapy need to be individually weighed against the more limited survival benefits in this population.

Salvage treatment

About one third of patients with PCNSL will present with disease that is refractory to first-line treatment and half of responders will relapse despite high response rates seen with initial treatment. The prognosis of progressive or relapsed PCNSL remains poor with limited treatment options. Salvage treatments for relapsed or refractory PCNSL patients depend on age, performance status, site of relapse within the CNS, prior treatments and time duration from last response. If the patient did not receive any consolidating treatment after the HD MTX-based induction chemotherapy, WBRT or HDC/ASCT should be considered. Two retrospective studies have evaluated WBRT delivered in relapsed PCNSL and reported a high rate of objective responses and a short median survival of 11-16 months - quite similar to what is expected with WBRT alone as initial treatment (Class IIIb).^{89,90} Delayed neurotoxicity occurred in 15%–22% of patients. However, in the setting of recurrence, WBRT did not prolong survival compared with non-WBRT-based therapies in the G-PCNSL-SG-1 trial (Class IIIa).²⁰ HDC/ASCT is an efficient alternative option, as has been previously discussed, and which should be preferentially proposed for patients aged < 60-65 years and with a tumour sensitive to second-line chemotherapy (Class IIb) (see section above).⁶⁶⁻⁶⁸ Otherwise, if the patient is not suitable for WBRT or HDC/ASCT, conventional chemotherapy can be proposed as second-line treatment. There is however, only a limited number of prospective studies available for guidance and these have been single-arm phase II trials complicating any comparison across trials (Class IIb, III and IV for all studies in this section). Several drugs used as single agent or in combination, with or without rituximab, have been evaluated and demonstrated modest activity such as temozolomide,^{38,91} topotecan,⁹² pemetrexed,⁹³ bendamustine,⁹⁴ PCV regimen,⁹⁵ ifosfamide-etoposide based regimen,^{37,96} or cisplatin-cytarabine based regimen.⁹⁷ MTX rechallenge given as single agent or in combination may also yield a high rate of new objective response and durable remission in patients who previously achieved prolonged response with HD MTX-based chemotherapy, suggesting retained chemosensitivity to MTX (Class III).^{98,99} Extra-CNS relapses account for 7% of failures, and some studies suggest that extra-CNS relapses are associated with a better prognosis than CNS-involving relapses;¹⁰⁰ the best salvage treatment for this condition remains to be defined, but excellent results have been reported with anthracycline-based chemotherapy consolidated or not with HDC/ASCT.²⁸

Conclusions

Guidelines reflect the state of knowledge at a given timepoint. The EANO website will inform of future updates on this guideline (<https://www.eano.eu>).

Contributors

KHX chaired the task force. Based on best available evidence from literature review, the writing group (EB, JB, AH, KHX, MP, RR, US, TS, CS) produced the draft guideline, which was subsequently submitted to the review committee (UA, NC, MD, CD, AF, FG, RH, UH, RS, MT, MW). The revised guideline, taking into account the comments of the reviewers, was resubmitted by the chairman to the whole task force for review and amendments twice.

Declaration of interest

KHX was the principal investigator of a trial investigating temozolomide (Scherring-Plough) in PCNSL and declare no competing interest. UA reports personal fees from Varian and BrainLAB AG outside the submitted work. MP reports grants from GSK, Roche, Böhringer-Ingelheim, personal fees from GSK, Roche, BMS, outside the submitted work. US reports personal fees from Roche, Medac, GSK, outside the submitted work. MT reports honoraria ad hoc consultancy for Hoffmann La Roche, outside the submitted work. MW reports grants and personal fees from Roche, Merck Serono, Isarna, Novocure, grants from Bayer, Piquar, personal fees from Celldex, Magforce, outside the submitted work. EB, JB, FG, AH, NC, RR, AJMF, MD, CD, TS, RS, CS, declare no competing interest.

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Table 1: Consensus statements and recommendations for the general approach to patients with PCNSL including establishment of diagnosis, baseline work-up and response to treatment

Diagnosis

- Cranial MRI with FLAIR and T1 weighted sequences before and after contrast injection is the neuroimaging method of choice for the diagnosis and follow-up of PCNSL. Diffusion, dynamic susceptibility contrast, proton spectroscopy MRI, and FDG-PET can be useful in the differential diagnosis but are not specific (Good Practice Point).
- The diagnosis of PCNSL requires pathological confirmation before treatment (Good Practice Point).
- When PCNSL is suspected, the standard surgical procedure for diagnosis is a stereotactic or navigation guided needle biopsy (Good Practice Point, see section on surgery for discussion).
- Because it may prevent the histopathological diagnosis, it is recommended, if clinically possible, to avoid steroids before biopsy. In case of remission and/or unspecific inflammation in the tissue biopsied in steroid-pretreated patients, rebiopsy is recommended when close and careful follow-up with serial MRI indicates further tumor growth (Good Practice Point).
- PCNSL are diagnosed according to the WHO classification. Immunohistochemistry is required (Good Practice Point, see pathology section in the webappendix).
- Required immunohistochemical markers for the lymphoma cell characterization should include: pan-B cell markers (CD19,CD20,PAX5), BCL6, MUM1/IRF4, CD10 (Good Practice Point).
- PCR analysis of immunoglobulin gene families may contribute to diagnosis in difficult cases, in particular when inflammatory disorders such as multiple sclerosis or corticosteroid-mitigated PCNSL are considered. (Good Practice Point).
- In case of a suspicion of PCNSL, the work-up should include at least an HIV blood test, a lumbar puncture (if not contraindicated) and an ophthalmologic evaluation (with a fundoscopy and a slit lamp examination) in all patients, including those without ocular symptoms (Good Practice Point).
- The identification of lymphoma cells in the CSF or the vitreous may obviate the need for a stereotactic brain biopsy to confirm the diagnosis only in the setting of high clinical and radiological suspicion of PCNSL. As cytologic diagnosis may be difficult, a review by a specialist pathologist is recommended, and in any doubt a brain biopsy is required (Good Practice Point).
- Immunophenotyping by multiparameter flow cytometry of cells collected in the CSF or vitreous and immediately analyzed may add to diagnostic sensitivity.
- if B-cell monoclonality is shown in a sample with atypical/suspicious cells. PCR based analysis of immunoglobulin gene rearrangement in the CSF reportedly may show false positives. Therefore, evidence for the clonality of the lymphocytic cell population considered separately remains insufficient for the diagnosis for PCNSL except in case of high clinically documented suspicion of PCNSL (Good Practice Point).

Staging

- Systemic staging should include: physical examination, CT-scan of the chest, abdomen and pelvis, testicular sonography and bone marrow biopsy. FDG body PET may represent an improved alternative to total body CT-scan and testicular sonography (Good Practice Point).

Prognosis

- Age and performance status have been consistently identified as treatment-independent prognostic factors in PCNSL. Evaluating the individual risk of a PCNSL patient before treatment according to one of the existing prognostic scores is recommended (Good Practice Point).
- Age over 60-65 is used to define the elderly population in PCNSL (Good Practice Point).

Evaluation of response and follow-up

- The International Primary CNS Lymphoma Collaborative Group (IPCG) criteria (2005) combining MRI, eye examination, CSF analysis and steroid dose should be used to evaluate response to treatment (Good Practice Point).
- There is no evidence as yet that brain FDG PET can be used to assess response in PCNSL in the way that it is used for other lymphomas (Good Practice Point).
- Formal prospective neuropsychometric testing is recommended in the follow-up of patients treated in clinical trials on PCNSL (Good Practice Point).

Table 2: Consensus statements and recommendations for treatment of patients with PCNSL

Surgery

- Surgical resection may be considered in patients suffering from a large space occupying lesion with acute symptoms of brain herniation to reduce rapidly intracranial pressure (Good practice point).
- In patients with an unifocal and resectable lesion suspected of PCNSL, no consensus was met in the panel to recommend either surgical resection or biopsy

Chemotherapy

- CHOP-regimens and derivatives are not indicated in PCNSL (Level B).
- Chemotherapy should include MTX at HD ($\geq 3\text{g/m}^2$) both to cross the BBB and yield cytotoxic levels in the CSF. It should be delivered in 2-3 hour iv infusions for a minimum of 4-6 injections and at intervals that should not exceed 2-3 weeks (Good Practice Point).
- Combination of HD-MTX with other chemotherapeutic agents improves the response rates with respect to HD-MTX alone (Level B).
- Chemotherapeutic agents to combine with HD MTX should be selected among active drugs known to cross BBB, such as HD cytarabine (Level B).
- HD-MTX-chemotherapy is feasible in elderly patients with adequate performance status and renal function (Level B).
- BBBD followed by IA MTX is an alternative experimental approach appropriated for a selected group of patients that should be undertaken by trained teams only (Level B).
- The value of IT chemotherapy as prophylaxis is unclear. IT chemotherapy (intralumbar or preferably intraventricular through an Ommaya reservoir) can be proposed in case of documented meningeal involvement with insufficient response to iv HD MTX ($>3\text{g/m}^2$) based chemotherapy (Good Practice Point).
- Rituximab combined with a chemotherapy regimen is still an experimental regimen that has its main place in clinical trials (Level C).

Radiotherapy

- WBRT, HD MTX, and *a fortiori* combined treatment expose patients to an increased risk of neurotoxicity (Level A).
- The role of consolidation WBRT following HD-MTX based chemotherapy remains debated. In addition, the optimal dose is not yet defined, but it should be chosen on the base of response to primary chemotherapy (Good Practice Point).
- In patients with progressive or residual disease after primary chemotherapy, a total dose of 40-45 Gy with a 1.8-2 Gy dose /fraction appears advisable. With such doses, there is no evidence to add a focal boost on the enhancing lesions (Good Practice Point).
- In patients < 60 years who have achieved a CR to induction chemotherapy, the option of immediate WBRT (40 - 45 Gy in 1.8 - 2.0 Gy fractions) or WBRT omission should be discussed with the patient. Reduced dose WBRT consolidation (23.4 - 30 Gy in 1.8 - 2.0 Gy fractions) is a therapeutic option that should be investigated in a clinical trial (Good Practice Point).
- In patients > 60 years, the risk of delayed neurotoxicity, after WBRT (doses >30 Gy in 1.8-2.0 Gy fractions) especially if following HDMTX , is unacceptably high and WBRT at this dose should be deferred or avoided (Level B).

High dose chemotherapy with autologous stem cell transplantation (HDC/ASCT)

- HDC/ASCT is an efficient treatment in relapsed or refractory PCNSL (Level B).
- HDC/ASCT should be reserved for patients < 60-65 years (Good Practice Point).
- High-dose thiotepa-based conditioning chemotherapy should be preferred over the BEAM regimen (Level C).
- HDC/ASCT as consolidation in first-line treatment remains experimental in PCNSL and should be restricted by selected trained centers (Good Practice Point).

Primary intraocular lymphoma (PIOL)

- PIOL may be treated by either HD-MTX-based chemotherapy (with or without WBRT) or by local therapy (intravitreal chemotherapy or ocular RT) (Good Practice Point).
- Local treatment (intravitreal chemotherapy or ocular RT) is a valid approach for patients with systemic chemotherapy contraindications or for elderly patients with relapsing intraocular disease (Good Practice Point).
- Concurrent intraocular and CNS lymphoma should be treated no differently from PCNSL (Good Practice Point).
- If consolidation WBRT is proposed, it should include both eyes (Good Practice Point).

- Refractory and relapsed IOL should be treated according to the patients' characteristics and prior treatments. Treatments include intravitreal injections of MTX, focal radiotherapy, WBRT, systemic chemotherapy and HDC/ASCT (Good Practice Point).

Salvage treatment

- Patients with relapsed / refractory PCNSL should be enrolled into phase I-II trials (Good Practice Point).
- The choice of the most appropriate salvage treatment should depend upon the patient's age, performance status, comorbidity, site of relapse, prior therapy, and duration of previous response. The expected side effects of the chosen drug must also be considered carefully (Good Practice Point).
- Salvage WBRT may be proposed in radiotherapy-naïve patients; it may be preceded by induction chemotherapy (Good Practice Point)
- HDC/ASCT is a valid therapeutic option in patients aged <60-65 years with chemosensitive relapsing PCNSL (Level B).
- Salvage chemotherapy can be delivered as induction therapy before WBRT or HDC/ASCT, or as exclusive treatment in patients not eligible for these therapies.
- MTX re-challenge should be considered in recurrent PCNSL patients who previously responded to HD MTX (Level C).
- Isolated extra-CNS relapses should be managed with anthracycline-based chemotherapy followed or not by HDC/ASCT (Good Practice Point)

WEBAPPENDIX

This webappendix summarizes evidences used for EANO's recommendations for the general approach to PCNSL patients with coverage of diagnostic aspects – pathology and genetics, clinical presentation, pathological confirmation, neuropathology of corticosteroid-treated PCNSL, cerebrospinal fluid (CSF) analyses, vitreous analyses, staging, – as well as prognostic factors, response criteria to treatment, treatment related neurotoxicity and treatment of intraocular lymphoma.

Pathology and genetics

PCNSL is a mature B cell lymphoma corresponding to DLBCL of the CNS. Morphologically, haematopoietic tumor cells, mostly resembling centroblasts, are scattered throughout the brain tissue and also exhibit a marked angiotropism with sheets of tumor cells clustering within and around blood vessel wall. Immunohistochemistry is required for the diagnosis. In addition to the expression of pan-B cell markers (CD19, CD20, PAX5), the tumor cells of PCNSL are characterized by a BCL6⁺IRF/MUM1+CD10⁻ immunophenotype with high proliferative activity (Ki-67 indexes of 70-90%), together with high expression of the MYC and BCL2 proteins.¹⁻³ With rare exception, Epstein-Barr Virus (EBV) is absent from PCNSL of immunocompetent patients. Ongoing activity of the germinal center program and blocked terminal B cell differentiation together with pathways deregulated by genetic alterations (B cell receptor, toll like receptor, NF-κB pathways) may foster B cell activation and brisk proliferation and be of pathogenetic relevance.⁴⁻⁹ Analysis of the molecular landscape of PCNSL indicates that aberrant somatic hypermutation which targets several genes (*PIM1*, *TTF*, *MYC*, *KLH14*, *OSPL10*, *SUSD2*) may play an important role in the pathogenesis of PCNSL,^{9,10} and that alterations in genes of role in CNS development may facilitate DLBCL manifestation in the CNS.¹⁰ Epigenetic studies revealed frequent gene silencing due to CpG island hypermethylation in individual genes including *MGMT*, *CDKN2A*, and *DAPK*.^{11,12} Recurring chromosomal losses affected the 6q, 6p21.32 (*HLA* locus) and 9p21 (*CDKN2A* locus) regions.^{5,13} However, to date, no specific molecular genetic signature distinguishes clearly PCNSL from non-CNS DLBCL, suggesting an important role of the microenvironment in explaining the peculiar behaviour of PCNSL. For research, collecting frozen samples and developing a network for PCNSL tumor banks should be encouraged.

Diagnosis

Clinical presentation

Presenting symptoms may include cognitive decline and/or personality changes, focal neurological deficits and increased intracranial pressure. Seizures are less frequent (10%). Ocular symptoms, due to an involvement of retina, choroid or vitreous, are represented by floaters and/or blurred vision; they can be either isolated (10%) or coexist with cerebral symptoms (10-20%). However, up to one-half of patients with PCNSL and ocular involvement have no visual symptoms. Insidious onset and delayed diagnosis of intraocular lymphoma are common.¹⁴ In immunocompetent patients, cranial MRI with contrast enhancement typically shows intense and homogeneously enhancing single lesions (70%) or multiple lesions (30%) with modest surrounding edema, usually located in periventricular areas and/or deep gray matter.^{15,16} Although suggestive, all these MRI findings are not specific. Advanced imaging techniques, especially FDG-PET, diffusion tensor imaging, dynamic susceptibility contrast MRI (DSC-MRI) and proton MR spectroscopy can increase the diagnostic accuracy and help in differentiating PCNSL from other brain tumors or non-tumor lesions.¹⁷⁻²⁶ However, although some signatures are highly suggestive of PCNSL, especially when present together (low regional cerebral blood volume ratios, high percentage of signal-intensity recovery at the end of the first pass of contrast agent relative to baseline, very high lipid resonances), they are not sufficiently specific in practice to replace pathological confirmation.

Pathological confirmation

Diagnosis always needs to be confirmed pathologically, according to the WHO classification in most cases by stereotactic needle biopsy.¹ In classical cases, combined histology and immunohistochemistry yields the diagnosis of PCNSL, i.e. DLBCL of the CNS. In such cases, molecular studies are not required. In equivocal cases PCR testing for clonality may aid the diagnosis.^{27,28}

Neuropathology of corticosteroid-treated PCNSL

As the tumor cells of PCNSL are potentially highly sensitive to corticosteroids, they may undergo rapid apoptosis. Transient tumor shrinkage or disappearance of contrast enhancement may occur even after short

exposure to steroids in approximately 40% of PCNSL, coupled with significant neurological improvement.²⁹ Stereotactic or navigation guided needle biopsy in this setting may be non-diagnostic in up to 50% of cases.³⁰ In the absence of tumor blasts, resorptive changes with prominent infiltration of macrophages, T cells, reactive astrocytes, and prominent microglial activation may prevail. In some cases, a few enlarged B cells may persist, being suspicious of blast. In such cases, PCR analysis of immunoglobulin genes may demonstrate monoclonality. However, a small number of B cells may pretend monoclonality ("pseudoclonality"). Therefore, unless patients are rapidly deteriorating with suggestive radiological features of PCNSL, it is usually recommended to defer corticosteroids until histologic confirmation has been obtained. Clinicians referring from peripheral hospitals should discuss with the specialist neurosurgical centre before starting corticosteroids. If, nevertheless, corticosteroids have been given with a subsequent objective response, tapering corticosteroids within one or two weeks and delaying biopsy until tumor regrowth would be a reasonable option. Since regrowth occur in most cases within a few weeks after discontinuation corticosteroids, a serial MRI follow-up with one month interval may be recommended at least the first three months. If no significant changes in contrast enhancement or progression are observed, biopsy seems associated with a relatively good probability of yielding a diagnosis despite steroid pre-treatment.³¹

CSF analysis

The identification of lymphoma cells in the CSF or in a vitreous biopsy, when possible, may obviate the need for a brain biopsy for the diagnostic confirmation, only in the setting of high clinical and radiological suspicion of PCNSL. Frequently, CSF is characterized by elevated protein levels in 75% and mild pleiocytosis in 50% of patients. However, lymphoma cells are detected in only 10-30% in the CSF.^{32,33} Cellular immunophenotyping by flow cytometry in the CSF and PCR analysis of immunoglobulin heavy and light chain genes may help to distinguish malignant cells from reactive lymphocytes by identifying clonal B-cell populations even when cytological examination is negative.^{34,35} However, low cell numbers in the CSF sample are frequently found and may make flow cytometric analysis difficult. A relatively high ratio of PCR false negatives has been reported in PCNSL.^{33,36} Different CSF molecular genetic markers and proteins including microRNA (miR-21, miR-19b, and miR-92),³⁷ soluble CD19,³⁸ antithrombin III,³⁹ free immunoglobulin light chains,⁴⁰ and interleukin-10 and CXCL13,⁴¹ are potentially useful diagnostic biomarkers for PCNSL but require further validation before being used in routine practice. As cytologic diagnosis may be difficult, in any doubt or inconsistencies with the patient clinical setting, a pathological confirmation by a brain biopsy is recommended.

Vitreous analysis

Ophthalmologic evaluation includes fundoscopy and slit lamp examination. Fluorescein angiography may be useful for lymphomatous involvement of the retina.¹⁴ Ophthalmologic involvement has to be confirmed by vitreous biopsy when eyes are the unique site of disease. Positive cytology is obtained in 70% of cases in trained pathology department. As for CSF, immunophenotyping and detection of IgH or T-cell receptor rearrangements by PCR analysis indicating monoclonality are helpful tools for diagnosis.^{42,43} High levels of interleukin 10 (IL10) and/or high IL10 / IL6 ratio in ocular fluids are strongly suggestive of B-cell lymphomatous uveitis,⁴⁴ but are not diagnostic.

Staging

The aims of staging are both to specify the extent of the lymphoma within the CNS and to exclude the presence of the disease elsewhere. If not contraindicated and already performed at the diagnostic work-up, all patients should have a lumbar puncture for CSF cytology. Systemic involvement is present in up to 12% of the cases.^{45,46} Since identification of a systemic site of the lymphoma has important implications for the treatment strategy, an international workshop to standardize baseline evaluation recommended performing at least a CT-scan of the chest, abdomen and pelvis, a bone marrow biopsy, a testicular ultrasound in elderly males.⁴⁷ FDG body PET, which is more sensitive than the body CT-scan,⁴⁸ is not yet an established routine diagnostic investigation, but is used in some European countries as an integral part of diagnostic work-up.

Prognostic factors

Age and performance status have been consistently recognized as the most important therapy-independent prognostic factors.⁴⁹⁻⁵³ Based on retrospective cohorts of PCNSL, other variables including serum lactate dehydrogenase (LDH) levels, involvement of deep brain structures,⁵³⁻⁵⁵ CSF protein levels,^{50,53} and extent of lesions within the CNS (multifocal versus unifocal),⁵² have been correlated with outcome, and some of them are integrated with age and performance status in different prognostic scoring systems. Hence, three clinically meaningful prognostic scores are available for PCNSL: the IELSG score,⁵³ the MSKCC score,⁵¹ and the Nottingham-Barcelona score.⁵² All of them distinguished 3 different risk groups. Using such scoring systems is useful to compare studies in order to avoid as much as possible selection biases. Since then, other prognostic

factors have been correlated with unfavorable outcome and need to be validated in independent series: elevated FDG uptake on PET,⁵⁶ chromosome 6q deletion or *CDKN2A* homozygous deletion in the tumor DNA,^{5,57} and delayed response to initial chemotherapy, as compared to early response.⁵⁸ Several variables have yielded opposite results in retrospective studies, such as apparent diffusion coefficient (ADC) value derived from diffusion-weighted imaging,⁵⁹⁻⁶¹ BCL-6 expression analysis,⁶²⁻⁶⁶ and MTX exposure reflected by MTX area under the curve (AUC).⁶⁷⁻⁷⁰

Response criteria

In 2005 the International Primary CNS Lymphoma Collaborative Group (IPCG) published a consensus opinion to standardize response criteria and outcome measures in immunocompetent patients with PCNSL.⁴⁷ These response criteria define CR as complete disappearance of contrast enhancement on MRI, no evidence of ocular lymphoma, negative CSF cytology and discontinuation of corticosteroid use for at least 2 weeks prior to the evaluation of response. Since corticosteroids may mask presence of residual disease its discontinuation is included as an essential requirement. The IPCG also delineated which findings are compatible with unconfirmed CR (CRu). It is important to sort out CRu from PR because the latter means failure of primary treatment. According to the IPCG outline CRu includes those cases who fulfill the criteria for CR with the following limitations: at time of evaluation the patient is still on any dose of corticosteroids, MRI continues to show small but persistent enhancing abnormalities related to biopsy/surgical site or to focal hemorrhage, and the follow-up ophthalmologic examination shows persistent minor abnormality which is unlikely to represent ocular lymphoma. PR is defined as 50% decrease in enhancing tumor or residual disease on eye examinations, or persistent or suspicious CSF cytology. Progressive disease (PD) is recognized as 25% increase in the enhancing lesion or appearance of any new site of disease in the CNS or as systemic disease, recurrent or new ocular disease, or recurrent or positive CSF cytology. Of note, these definitions do not take into account the non-enhancing lesion best visualized on T2-Flair MRI, whose differential diagnosis may be challenging since it could be treatment-related white matter changes (including leukoencephalopathy) but also correspond to infiltrative PD.⁷¹ There is no evidence as yet that brain FDG PET can be used to assess response in PCNSL in the way that it is used for other lymphomas.

Delayed neurotoxicity

Delayed treatment-related neurotoxicity has been systematically evaluated in few studies (Class II and III). However, there is a general perception and agreement, that the combination of HD MTX and WBRT is associated with disabling neurotoxicity with an incidence of 25% to 35% and related mortality of 30%.^{50,72} This deleterious treatment complication typically occurs several months to years after successful treatment. Neuropsychological examination may confirm impaired psychomotor speed, executive function, attention and memory.⁷³ Affected patients show cortical/subcortical atrophy and leukoencephalopathy,⁷³⁻⁷⁵ which may leave them demented, ataxic and incontinent. Median survival after onset of clinically-evident neurotoxicity is less than 1-2 years.^{50,72,75} Autopsy findings include myelin and axonal loss, gliosis, spongiosis, thinning of white matter, small and large vessel disease, and necrosis.^{75,76} Of note, imaging abnormalities may not always correlate with the neurologic impairment severity over time. In a retrospective mono-institutional series analysis of 183 patients, only the administration of WBRT was identified as an independent risk factor for the development of late neurotoxicity: in this series, 2% treated with chemotherapy alone developed clinically-evident neurotoxicity, while 33% treated with combination chemo-/radiotherapy were affected. The cumulative incidence of neurotoxicity for the whole group was 5% at 2 years and 24% at 5 years, with a substantially higher risk in patients ≥ 60 years (Class IIb).⁷⁵ They are related to clinically and radiologically overt neurotoxicity. The prevalence of treatment-related "subtle" cognitive dysfunction amongst patients treated for PCNSL is probably largely underestimated as formal psychometric evaluations have not been routinely performed in most prospective studies. Small case series identified WBRT, and not chemotherapy, as the primary cause of neurotoxicity in PCNSL.^{76,77} These results have been confirmed by 3 long-term evaluations (Class IIb).⁷⁸⁻⁸⁰ In the most recent analysis of 80 long-term survivors of PCNSL, free of tumor and having completed treatment with different regimens at least two years prior to evaluation, those who had received WBRT showed significantly lower mean scores in attention and executive function, motor skills, and neuropsychological composite score, associated with poorer quality of life measures (Class IIb).⁸⁰ Moreover, on brain imaging, mean areas of total T2 abnormalities in the WBRT group were more than twice the mean of any other non-WBRT group. These results caution against the routine administration of WBRT as part of upfront treatment and call for the implementation of formal neuropsychometric testing in clinical trials on PCNSL.⁷³

Intraocular lymphoma

Intraocular infiltration can be the exclusive site of disease at presentation, the so-called primary intra-ocular lymphoma (PIOL), or as a part of PCNSL with concomitant brain or meningeal disease. The optimal treatment for intraocular lymphoma is not known. Data on therapy and outcome are scarce and limited to retrospective case reports or mostly small series with heterogeneous patient populations and treatments. As many as 90 % of patients with PIOL patients consequently develop brain involvement over the course of the disease and dissemination to the brain is the main cause of death.^{14,81} The median survival of isolated PIOL is approximately 60 months.^{81,82} Treatment may be focal, including ocular RT (historically, total dose of 35-40 Gy, 2 Gy per fraction using opposed lateral beams to include both globes) (Class IV) and intravitreal chemotherapy.⁸³⁻⁸⁶ Uncontrolled series have reported clinical remission with repeated intravitreal MTX and more recently after rituximab injections (Class IV).^{85,86} Treatment may be also extensive, including systemic chemotherapy and WBRT. Intraocular responses have been reported with HD MTX,⁸⁷ HD cytarabine,^{88,89} ifosfamide, trofosfamide used as single agent,⁹⁰ with MTX-based polychemotherapy and after HDC/ASCT (Class IV).⁹¹ A large retrospective multicenter study did not show any difference in PIOL between focal and extensive therapy in terms of disease control and survival (Class IIb).⁸¹ Unfortunately, this and other studies failed to provide reliable predictors of brain dissemination in PIOL patients; thus, some experts recommend local therapy for disease confined to the eyes, but others consider that initial treatment of PIOL should not differ from that of PCNSL i.e. high-dose MTX-based polychemotherapy followed, or not, by WBRT in order to eradicate possible concomitant microscopic disease in the brain and in the CSF responsible for relapse. In this case, local treatments would remain options for refractory or recurrent disease confined to the eyes. The management decision should take into account the individual risk of treatment toxicities (including those related to ocular treatment) and local expertise.^{14,92} When intraocular lymphoma is concurrent with brain lesions, it has not been identified as an independent prognostic factor and the prognosis is similar to that of the PCNSL without intraocular disease (Class IIb).⁹³ Accordingly, patients with concomitant intraocular and cerebral disease should be treated no differently from PCNSL. The value of additional local ocular treatment (i.e. intravitreal chemotherapy or ocular radiotherapy if WBRT has not been delivered) to systemic chemotherapy remains matter of debate, with conflicting results in two retrospective studies (Class IIb).^{93,94}

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